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OIPE JC26 JAN 15 2002 PATENT & TRADEMARK OFFICE

F. Aaron Dubberley
(Print Name)

Date: DECEMBER 18, 2001

(Signature)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Group No.: 1623

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JAN 22 2002
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In re application of:

Jean Ackermann, et al.

Serial No.: 09/925,188

Filed: August 09, 2001

For: **2,3-OXIDOSQUALENE-LANOSTEROL CYCLASE INHIBITORS**

TRANSMITTAL OF CERTIFIED COPIES

December 18, 2001

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Attached please find the certified copies of the foreign applications from which priority is claimed for this case:

Country	Application No.	Filing Date
Europe	00117611.4	August 16, 2000
Europe	01113646.2	June 19, 2001

Respectfully submitted,

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Enclosures
54020

Eur päisches Patentamt | European Patent Office | Office eur péen des brevets

Bescheinigung | Certificate | Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

00117611.4

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
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Blatt 2 der Bescheinigung
Sh et 2 of the certificate
Page 2 de l'attestation

Anmeldung Nr.:
Application no.: 00117611.4
Demande n°:

Anmeldetag:
Date of filing: 16/08/00
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
F. HOFFMANN-LA ROCHE AG
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SWITZERLAND

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:
Novel aminocyclohexane derivates

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat: State: Pays:	Tag: Date: Date:	Aktenzeichen: File no. Numéro de dépôt:

Internationale Patentklassifikation:
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Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR
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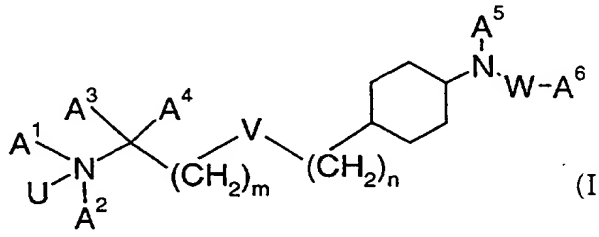
F. Hoffmann-La Roche AG, CH-4070 Basle, Switzerland

Case 20739

Novel Aminocyclohexane Derivatives

The present invention is concerned with novel aminocyclohexanol derivatives, their manufacture and their use as medicaments. In particular, the invention relates to compounds of the formula (I)



(I)

wherein

U		is O or a lone pair,
V		is O, S, $-CH_2-$, -CH=CH-, or $-C\equiv C-$,
W		is CO, COO, $CONR^1$, CSO, $CSNR^1$, SO_2, or SO_2NR^1,
m and n		independently from each other are 0 to 7 and m+n is 0 to 7, with the provisio that m is not 0 if V is O or S,
A^1		is H, lower-alkyl, hydroxy-lower-alkyl, or lower-alkenyl
A^2		is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, or lower-alkenyl, optionally substituted by R^2,
A^3 and A^4		are hydrogen or lower-alkyl, or

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A^1 and A^2 or A^1 and A^3 are bonded to each other to form a ring and - A^1- A^2- or - A^1- A^3- are lower-alkylene or lower-alkenylene, optionally substituted by R^2, in which one -CH_2- group of -A^1- A^2- or -A^1-A^3- can optionally be replaced by NR^3, S, or O,

A^5 is H, lower-alkyl, lower-alkenyl, or aryl-lower-alkyl,

A^6 is lower-alkyl, cycloalkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, lower-alkoxy-carbonyl-lower-alkyl,

R^2 is hydroxy, hydroxy-lower-alkyl, lower-alkoxy, lower-alkoxycarbonyl, $N(R^4,R^5)$, or thio-lower-alkoxy,

R^1, R^3, R^4 and R^5 independently from each other are hydrogen or lower-alkyl,

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

The compounds of the present invention inhibit 2,3-oxidosqualene-lanosterol cyclase (EC 5.4.99.) which is required for the cholesterol and ergosterol biosynthesis. Causal risk factors that directly promote the development of coronary and peripheral atherosclerosis include elevated low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), hypertension, cigarette smoking and diabetes mellitus. Other synergistic risk factors include elevated concentrations of triglyceride (TG)-rich lipoproteins, small, dense low-density lipoprotein particles, lipoprotein (a) (Lp(a)), and homocysteine. Predisposing risk factors modify the causal or conditional risk factors and thus affect atherogenesis indirectly. The predisposing risk factors are obesity, physical inactivity, family history of premature CVD, and male sex. The strong connection between coronary heart disease (CHD) and high LDL-C levels in plasma, and the therapeutic advantage of lowering elevated LDL-C levels are now well established (Gotto et al., Circulation 81, 1990, 1721-1733; Stein et al., Nutr. Metab. Cardiovasc. Dis. 2, 1992, 113-156; Illingworth, Med. Clin. North. Am. 84, 2000, 23-42). Cholesterol-rich, sometimes unstable, atherosclerotic plaques lead to the occlusion of blood vessels resulting in an ischemia or an infarct. Studies with respect to primary prophylaxis have shown that a lowering of plasma LDL-C levels in plasma reduces the frequency of non-fatal incidences of CHD, while the overall morbidity remains unchanged. The lowering of plasma LDL-C levels in patients with preestablished CHD (secondary intervention) reduces CHD-mediated mortality and morbidity; metaanalysis of different studies shows that this decrease is proportional to the reduction of the LDL-C (Ross et al., Arch. Intern. Med. 159, 1999, 1793-1802).

The clinical advantage of cholesterol lowering is greater for patients with

preestablished CHD than for asymptomatic persons with hypercholesterolemia. According to current guidelines patients who had survived a myocardial infarct or patients suffering from angina pectoris or another atherosclerotic disease a cholesterol-lowering treatment is recommended, with a target LDL-C level of 100 mg/dl.

Preparations such as bile acid sequestrants, fibrates, nicotinic acid, probucol as well as the statins (HMG-Co-A reductase inhibitors) such as simvastatin and atorvastatin are used for usual standard therapies. The best statins reduce LDL-C effectively by at least 40%, and also triglycerides, a synergistic risk factor, but less effectively. In contrast, fibrates reduce triglycerides effectively, but not LDL-C. Combination of a statin and a fibrate proved to be very efficacious in lowering LDL-C and triglycerides (Ellen and McPherson, J. Cardiol. 81, 1998, 60B-65B), but safety of such a combination remains an issue (Shepherd, Eur. Heart J. 16, 1995, 5-13). A single drug with a mixed profile combining effective lowering of both LDL-C and triglycerides would provide additional clinical benefit to asymptomatic and symptomatic patients.

In humans, statins are well tolerated at standard dosage, but reductions in non-sterol intermediates in the cholesterol synthesis pathway, such as isoprenoids and coenzyme Q, may be associated with adverse clinical events at high doses (Davignon et al., Can. J. Cardiol. 8, 1992, 843-864; Pederson and Tobert, Drug Safety 14, 1996, 11-24).

This has stimulated the search for and development of compounds that inhibit cholesterol biosynthesis, yet act distal to the synthesis of these important, non-sterol intermediates. 2,3-oxidosqualene:lanosterol cyclase (OSC), a microsomal enzyme, represents a unique target for a cholesterol-lowering drug (Morand et al., J. Lipid Res., 38, 1997, 373-390; Mark et al., J. Lipid Res. 37, 1996, 148-158). OSC is downstream of farnesyl-pyrophosphate, beyond the synthesis of isoprenoids and coenzyme Q. In hamsters, pharmacologically active doses of an OSC inhibitor showed no adverse side-effects, in contrast to a statin which reduced food-intake and body weight, and increased plasma bilirubin, liver weight and liver triglyceride content (Morand et al., J. Lipid Res., 38, 1997, 373-390). The compounds described in European Patent Application No. 636 367, which inhibit OSC and which lower the total cholesterol in plasma, belong to these substances.

OSC inhibition does not trigger the overexpression of HMGR because of an indirect, negative feed-back regulatory mechanism involving the production of 24(S),25-epoxycholesterol (Peffley et al., Biochem. Pharmacol. 56, 1998, 439-449; Nelson et al., J. Biol. Chem. 256, 1981, 1067-1068; Spencer et al., J. Biol. Chem. 260, 1985, 13391-13394; Panini et al., J. Lipid Res. 27, 1986, 1190-1204; Ness et al., Arch. Biochem. Biophys. 308, 1994, 420-425). This negative feed-back regulatory mechanism is fundamental to the

concept of OSC inhibition because (i) it potentiates synergistically the primary inhibitory effect with an indirect down-regulation of HMGR, and (ii) it prevents the massive accumulation of the precursor monooxidosqualene in the liver. In addition, 24(S),25-epoxycholesterol was found to be one of the most potent agonists of the nuclear receptor LXR (Janowski et al., Proc. Natl. Acad. Sci. USA, 96, 1999, 266-271). Considering that 24(S),25-epoxycholesterol is a by-product of inhibition of OSC it is hypothesized that the OSC inhibitors of the present invention could also indirectly activate LXR-dependent pathways such as (i) cholesterol-7alpha-hydroxylase to increase the consumption of cholesterol via the bile acid route, (ii) expression of ABC1 and/or ABC8 proteins with the potential to stimulate reverse cholesterol transport and increase plasma HDL-C levels (Venkateswaran et al., J. Biol. Chem. 275, 2000, 14700-14707; Costet et al., J. Biol. Chem. June 2000, in press; Ordovas, Nutr Rev 58, 2000, 76-79), and/or inhibit intestinal cholesterol absorption (Mangelsdorf, XIIth International Symposium on Atherosclerosis, Stockholm, June 2000). In addition, possible cross talks between fatty acid and cholesterol metabolism mediated by liver LXR have been hypothesized (Tobin et al., Mol. Endocrinol. 14, 2000, 741-752).

The present compounds of formula I inhibit OSC and therefore also inhibit the cholesterol and ergosterol biosynthesis, and reduce the plasma cholesterol levels. They can therefore be used in the therapy and prophylaxis of hypercholesterolemia, hyperlipemia, arteriosclerosis and vascular diseases in general. Furthermore, they can be used in the therapy and/or prevention of mycoses, gallstones, tumors and hyperproliferative disorders. In addition, it has unexpectedly been found that the compounds of the present invention can also be of therapeutical use to improve glucose tolerance in order to treat and/or prevent related diseases such as diabetes. The compounds of the present invention further exhibit improved pharmacological properties compared to known compounds.

Unless otherwise indicated the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to seven, preferably of one to four carbon atom(s).

The term "lone pair" refers to an unbound electron pair, in particular to the unbound electron pair of a nitrogen atom in e.g. an amine.

The term "halogen" refers to fluorine, chlorine, bromine and iodine, with chlorine and bromine being preferred.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty

carbon atoms, preferably one to sixteen carbon atoms. Alkyl groups can be substituted e.g. with halogen, CN, NO_2, carboxy, and/or aryl. Other, more preferred subsituents are hydroxy, lower-alkoxy, NH_2, N(lower-alkyl)$_2$, and/or lower-alkoxy-carbonyl.

The term "lower-alkyl" , alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, t-butyl and the like. A lower-alkyl group may have a substitution pattern as described earlier in connection with the term "alkyl".

The term "cycloalkyl" refers to a monovalent carbocyclic radical of 3 to 10 carbon atom(s), preferably 3 to 6 carbon atoms. Cycloalkyl in which one or more -CH_2- group is replaced by O, S, NH or N(lower-alkyl) are referred to as "heterocycloalkyl".

The term "alkoxy" refers to the group R'-O-, wherein R' is an alkyl. The term "lower-alkoxy" refers to the group R'-O-, wherein R' is a lower-alkyl. The term "thio-alkoxy" refers to the group R'-S-, wherein R' is an alkyl. The term "thio-lower-alkoxy" refers to the group R'-S-, wherein R' is a lower-alkyl.

The term "alkenyl", alone or in combination with other groups, stands for a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 20, preferably up to 16 carbon atoms. The term "lower-alkenyl" refers to a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 7, preferably up to 4 carbon atoms, such as e.g. 2-propenyl. An alkenyl or lower-alkenyl group may have a substitution pattern as described earlier in connection with the term "alkyl".

The term "alkylene" refers to a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 20 carbon atoms, preferably 1 to 16 carbon atoms. The term "lower-alkylene" refers to a straight chain or branched divalent saturated aliphatic hydrocarbon group of 1 to 7, preferably 2 to 4 carbon atoms. An alkylene or lower-alkylene group may have a substitution pattern as described earlier in connection with the term "alkyl".

The term "alkenylene" refers to a straight chain or branched divalent hydrocarbon group comprising an olefinic bond and up to 20 carbon atoms, preferably up to 16 carbon atoms. The term "lower-alkenylene" refers to a straight chain or branched divalent hydrocarbon group comprising an olefinic bond and up to 7, preferably up to 4 C-atoms. An alkenylene or lower-alkenylene group may have a substitution pattern as described earlier in connection with the term "alkyl".

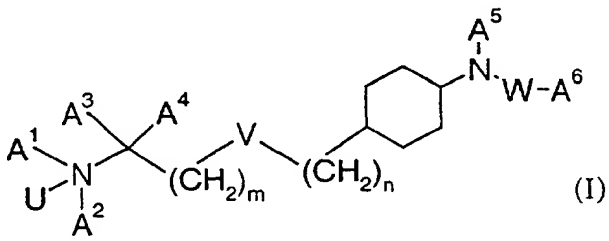
The term "aryl" relates to the phenyl or naphthyl group which can optionally be mono- or multiply-substituted by lower-alkyl, lower-alkyl-di-oxo, halogen, hydroxy, cyano, CF_3, NH_2, N(lower-alkyl)$_2$, aminocarbonyl, carboxy, nitro, lower-alkoxy, lower-alkylcarbonyl, lower-alkylcarbonyloxy, aryl, or aryloxy. Preferred substituents are lower-alkyl, lower alkoxy, lower-alkyl-carbonyl, lower-alkoxycarbonyl, fluorine, chlorine, bromine, CN, CF_3, NO_2, NH_2, and/or N(lower-alkyl)$_2$. More preferred substituents are fluorine, chlorine, bromine and CF_3.

The term "heteroaryl" refers to an aromatic 5- or 6-membered ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur such as furyl, pyridyl, 1,2-, 1,3- and 1,4-diazinyl, thienyl, isoxazolyl, oxazolyl, imidazolyl, or pyrrolyl. The term "heteroaryl" further refers to bicyclic aromatic groups comprising two 5- or 6-membered rings, in which one or both rings can contain 1, 2 or 3 atoms selected from nitrogen, oxygen or sulphur such as e,g, indol or chinolin, or partially hydrogenated bicyclic aromatic groups such as e.g. indolinyl. A heteroaryl group may have a substitution pattern as described earlier in connection with the term "aryl".

The term "pharmaceutically acceptable salts" embraces salts of the compounds of formula (I) with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, fumaric acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms. Preferred salts are formates, hydrochlorides and hydrobromides.

The term "pharmaceutically acceptable esters" embraces esters of the compounds of formula (I), in which hydroxy groups have been converted to the corresponding esters with inorganic or organic acids such as, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, p-toluenesulphonic acid and the like, which are non toxic to living organisms.

In detail, the present invention relates to compounds of formula (I)



(I)

wherein

U is O or a lone pair,

V is O, S, $-CH_2-$, -CH=CH-, or -C≡C-,

W is CO, COO, $CONR^1$, CSO, $CSNR^1$, SO_2, or SO_2NR^1,

m and n independently from each other are 0 to 7 and m+n is 0 to 7, with the provisio that m is not 0 if V is O or S,

A^1 is H, lower-alkyl, hydroxy-lower-alkyl, or lower-alkenyl

A^2 is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, or lower-alkenyl, optionally substituted by R^2,

A^3 and A^4 are hydrogen or lower-alkyl, or

A^1 and A^2 or A^1 and A^3 are bonded to each other to form a ring and $-A^1-A^2-$ or $-A^1-A^3-$ are lower-alkylene or lower-alkenylene, optionally substituted by R^2, in which one $-CH_2-$ group of $-A^1-A^2-$ or $-A^1-A^3-$ can optionally be replaced by NR^3, S, or O,

A^5 is H, lower-alkyl, lower-alkenyl, or aryl-lower-alkyl,

A^6 is lower-alkyl, cycloalkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, lower-alkoxy-carbonyl-lower-alkyl,

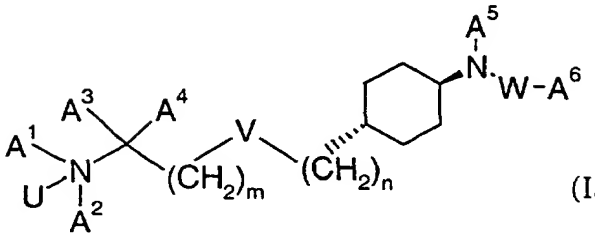
R^2 is hydroxy, hydroxy-lower-alkyl, lower-alkoxy, lower-alkoxycarbonyl, $N(R^4,R^5)$, or thio-lower-alkoxy,

R^1, R^3, R^4 and R^5 independently from each other are hydrogen or lower-alkyl,

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

Preferred are compounds of formula (I) and/or pharmaceutically acceptable salts thereof. Another preferred embodiment relates to compounds of formula (I) wherein U is a lone pair and a further preferred embodiment relates to compounds of formula (I) wherein U is O.

A further preferred embodiment of the present invention relates to the trans-form of the compounds as defined above characterized by formula (Ia)



(Ia)

wherein U, V, W, m, n, A^1, A^2, A^3, A^4, A^5 and A^6 have the significances given above.

Compounds as described above in which V is O, S, -C≡C-, or $-CH_2-$ relate to another preferred embodiment of the present invention. Compounds in which V represents O are particularly preferred as are compounds wherein V is $-CH_2-$.

Of the compounds of the present invention, those in which W represents CO, COO, $CONR^1$, $CSNR^1$, SO_2 or SO_2NR^1 and R^1 is hydrogen are preferred, with those wherein W represents COO or SO_2 being particularly preferred.

Compounds of the present invention in which n is 0 are preferred, as are those in which n is 1. Another preferred embodiment relates to compounds as defined above, wherein m is 1 to 6, or, if V is -C≡C-, m=0 is also preferred.

Other preferred compounds of the present invention are those in which A^1 represents H, methyl, ethyl, 2-hydroxy-ethyl or 2-propenyl. Another group of preferred compounds of the present invention are those in which A^2 represents lower-alkyl, cycloalkyl-lower-alky, or lower-alkenyl, optionally substituted with R^2, wherein R^2 is hydroxy, methoxy, or ethoxycarbonyl, with those compounds wherein A^2 represents methyl, ethyl, 2-hydroxy-ethyl, or 2-propenyl being especially preferred.

Compounds of formula (I), wherein A^1 and A^2 are bonded to each other to form a ring and $-A^1-A^2-$ is lower-alkylene, or lower-alkenylene, optionally substituted by R^2, in which one $-CH_2-$ group of $-A^1-A^2-$ can optionally be replaced by NR^3, S, or O, wherein R^2 and R^3 are as defined above are also preferred, with compounds wherein one $-CH_2-$ group of $-A^1-A^2-$ can optionally be replaced by O and wherein said optional substituent R^2 is hydroxy or 2-hydroxyethyl being particularly preferred. In compounds wherein A^1 and A^2 are bonded to each other to form a ring, said ring is preferrably a 4-, 5-, or 6-membered ring such as e.g. piperidinyl or pyrrolidinyl.

A further preferred embodiment of the present invention relates to compounds of formula (I), wherein A^3 and/or A^4 represent hydrogen. Compounds of formula (I), in which A^5 is H, lower-alkyl, lower-alkenyl, or benzyl optionally substituted with halogen are also preferred, with those wherein A^5 represents methyl or ethyl being especially preferred.

Compounds of formula (I), wherein A^6 is lower-alkyl, cycloalkyl, phenyl, naphthyl, phenyl-lower-alkyl, pyridyl, indolyl, indolinyl, thienyl, thienyl-methylene, furyl-methylene, benzodioxyl, chinolyl, isoxazolyl, or imidazolyl, optionally substituted by one or more substituents selected from the group consisting of lower-alkyl, lower-alkoxy, lower-alkylcarbonyl, lower-alkoxycarbonyl, fluorine, chlorine, bromine, CN, CF_3, NO_2, or $N(R^6,R^7)$, wherein R^6 and R^7 independently from each other are hydrogen or lower-alkyl are another preferred embodiment of the present invention, with those compounds wherein A^6 is phenyl optionally substituted by one or more substituents selected from the group consisting of fluorine, chlorine, bromine and CF_3, being more preferred, and with those compounds wherein A^6 is 4-chloro-phenyl, 4-bromo-phenyl or 4-trifluoromethyl-phenyl being particularly preferred.

Preferred compounds of general formula (I) are those selected from the group consisting of

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-nitro-phenyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid naphthalen-2-yl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid pentafluorophenylmethyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid benzyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid phenyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid p-tolyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-fluoro-phenyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid hexyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-methoxy-phenyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid isobutyl ester,

trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-

trifluoromethyl-phenyl ester,
trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester,
trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester,
trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-carbamic acid 4-fluoro-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-carbamic acid 4-fluoro-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
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trans-(4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-[4-(4-Diethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-[4-(4-Dimethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
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trans{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 2,4-difluoro-phenyl ester,

{4-[Trans-4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 3,4-difluoro-phenyl ester,
[trans-4-(4-Dimethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester,
(trans-4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 3,4-difluoro-phenyl ester,
[trans-4-(4-Diethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester,
ethyl-[trans-4-(4-piperidin-1-yl-butoxy)-cyclohexyl]-carbamic acid 3,4-difluoro-phenyl ester,
[trans-4-(4-Azetidin-1-yl-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester,
Methyl-[trans-4-(4-morpholin-4-yl-butoxy)-cyclohexyl]-carbamic acid 3,4-difluoro-phenyl ester,
Methyl-[trans-4-(4-pyrrolidin-1-yl-butoxy)-cyclohexyl]-carbamic acid 3,4-difluoro-phenyl ester,
(4-{trans-4-[Ethyl-(2-methoxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 3,4-difluoro-phenyl ester,
trans-5-Chloro-thiophene-2-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4,N-dimethyl-benzenesulfonamide,
trans-Naphthalene-2-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-methanesulfonamide,
trans-Quinoline-8-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-C-phenyl-methanesulfonamide,
trans-3,5-Dimethyl-isoxazole-4-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-Naphthalene-1-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-methoxy-N-methyl-benzenesulfonamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-fluoro-N-methyl-

benzenesulfonamide,
trans-Thiophene-2-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2-fluoro-N-methyl-benzenesulfonamide,
trans-1-Methyl-1H-imidazole-4-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-tert-butyl-N-methyl-benzenesulfonamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-butoxy-N-methyl-benzenesulfonamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-chloro-N-methyl-benzenesulfonamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-bromo-N-methyl-benzenesulfonamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-nitro-benzenesulfonamide,
trans-4-Bromo-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-benzenesulfonamide,
trans-N-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-4-Bromo-N-methyl-N-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-benzenesulfonamide,
trans-N-[4-(6-Azetidin-1-yl-hexyloxy)-cyclohexyl]-4-bromo-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-{4-[6-(butyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-methyl-N-[4-(6-piperidin-1-yl-hexyloxy)-cyclohexyl]-benzenesulfonamide,
trans-4-Bromo-N-{4-[6-(3,6-dihydro-2H-pyridin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-(4-{6-[ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-{4-[6-(3-hydroxy-pyrrolidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-methyl-N-{4-[6-(methyl-propyl-amino)-hexyloxy]-cyclohexyl}-benzenesulfonamide,

trans-4-Bromo-N-[4-(6-diallylamino-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-{4-[6-(4-hydroxymethyl-piperidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-(4-{6-[(2-hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-methyl-N-{4-[6-(4-methyl-piperidin-1-yl)-hexyloxy]-cyclohexyl}-benzenesulfonamide,
trans-4-Bromo-N-{4-[6-(4-hydroxy-piperidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-{4-[6-(cyclopropylmethyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide,
trans-[(6-{4-[(4-Bromo-benzenesulfonyl)-methyl-amino]-cyclohexyloxy}-hexyl)-methyl-amino]-acetic acid ethyl ester,
trans-N-[4-(6-Allylamino-hexyloxy)-cyclohexyl]-4-bromo-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-{4-[6-(2-hydroxy-ethylamino)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-[4-(6-ethylamino-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide,
trans-N-Methyl-N-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(6-Azetidin-1-yl-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[6-(Butyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-Methyl-N-[4-(6-piperidin-1-yl-hexyloxy)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[6-(3,6-Dihydro-2H-pyridin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{6-[Ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[6-(3-Hydroxy-pyrrolidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-Methyl-N-{4-[6-(methyl-propyl-amino)-hexyloxy]-cyclohexyl}-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(6-Diallylamino-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[6-(4-Hydroxymethyl-piperidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-4-

trifluoromethyl-benzenesulfonamide,
trans-N-(4-{6-[(2-Hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[6-(4-Hydroxy-piperidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[6-(Cyclopropylmethyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-[Methyl-(6-{4-[methyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-cyclohexyloxy}-hexyl)-amino]-acetic acid ethyl ester,
trans-[Methyl-(6-{4-[methyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-cyclohexyloxy}-hexyl)-amino]-acetic acid,
trans-N-[4-(6-Allylamino-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-chloro-N-methyl-benzenesulfonamide,
N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2,4-difluoro-N-methyl-benzenesulfonamide,
N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2-bromo-N-methyl-benzenesulfonamide,
N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-bromo-N-methyl-benzenesulfonamide,
N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2,4-dichloro-N-methyl-benzenesulfonamide,
N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-fluoro-N-methyl-benzenesulfonamide,
N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3,4-dichloro-N-methyl-benzenesulfonamide,
N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2-chloro-N-methyl-benzenesulfonamide,
N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3,4-difluoro-N-methyl-benzenesulfonamide,
trans-N-[4-(3-Allylamino-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}N-methyl4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxy}-cyclohexyl) N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(3-Diethylamino-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,

trans-N-(4-{3-[(2-Hydroxy-ethyl)-methyl-amino]-propoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{3-[Bis-(2-hydroxy-ethyl)-amino]-propoxy}-cyclohexyl) N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[3-(Cyclopropylmethyl-methyl-amino)-propoxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-Methyl-N-[4-(3-pyrrolidin-1-yl-propoxy)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(3-Ethylamino-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-Methyl-N-[4-(3-morpholin-4-yl-propoxy)-cyclohexyl]- 4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[3-(2-Hydroxy-ethylamino)-propoxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{3-[Ethyl-(2-methoxy-ethyl)-amino]-propoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[3-(3,6-Dihydro-2H-pyridin-1-yl)-propoxy]- cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-Methyl-N-{4-[3-(methyl-propyl-amino)-propoxy]- cyclohexyl}-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(4-Allylamino-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(4-Diethylamino-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(4-Dimethylamino-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{4-[(2-Methoxy-ethyl)-methyl-amino]-butoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{4-[(2-Hydroxy-ethyl)-methyl-amino]-butoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{4-[Bis-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[4-(Cyclopropylmethyl-methyl-amino)-butoxy]- cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(4-Ethylamino-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-

benzenesulfonamide,
trans-N-Methyl-N-[4-(4-morpholin-4-yl-butoxy)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[4-(2-Hydroxy-ethylamino)-butoxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[4-(3,6-Dihydro-2H-pyridin-1-yl)-butoxy]- cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-Methyl-N-{4-[4-(methyl-propyl-amino)-butoxy]- cyclohexyl}-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{4-[Ethyl-(2-methoxy-ethyl)-amino]-butoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{3-[(2-Methoxy-ethyl)-methyl-amino]-propoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
N-{4-trans-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-4-chloro-N-methyl-benzenesulfonamide,
N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-4-chloro-N-methyl-benzenesulfonamide,
N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-4-bromo-N-methyl-benzenesulfonamide,
N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-N-methyl-C-phenyl-methanesulfonamide,
N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-4-fluoro-N-methyl-benzenesulfonamide,
N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-2-fluoro-N-methyl-benzenesulfonamide,
N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-N-methyl-benzenesulfonamide,
5-Chloro-thiophene-2-sulfonic acid {4-trans-[4-(allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-amide,
trans-Pyridine-2-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-1H-Indole-2-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-chloro-N-methyl-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-fluoro-N-methyl-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-bromo-N-methyl-benzamide,

trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzamide,
trans-Thiophene-3-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-5-Bromo-thiophene-2-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-2-thiophen-3-yl-acetamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2-(2,4-difluoro-phenyl)-N-methyl-acetamide,
trans-5-Fluoro-1H-indole-2-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2-(4-fluoro-phenyl)-N-methyl-acetamide,
trans-1H-Indole-5-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-chloro-N-methyl-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-fluoro-3,N-dimethyl-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-nitro-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4,N-dimethyl-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-cyano-N-methyl-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3,N-dimethyl-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3,4-dimethoxy-N-methyl-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-methoxy-N-methyl-benzamide,
trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-fluoro-N-methyl-3-nitro-benzamide,
trans-4-Acetyl-N-{4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzamide,
trans-N-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzamide,
trans-N-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzamide,
trans-N-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-3-cyano-N-methyl-benzamide,
trans-N-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-4-bromo-N-methyl-

benzamide,
trans-N-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-4-bromo-N-methyl-benzamide,
trans-5-Bromo-thiophene-2-carboxylic acid {4-[4-(allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-amide,
trans-N-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-4-fluoro-N-methyl-benzamide,
trans-N-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-4-fluoro-N-methyl-benzamide,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(2,4-difluoro-phenyl)-1-methyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(2,4-dimethoxy-phenyl)-1-methyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-fluoro-phenyl)-1-methyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-methoxy-phenyl)-1-methyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-p-tolyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-methoxy-2-methyl-phenyl)-1-methyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(2,4-dimethyl-phenyl)-1-methyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-(3,4,5-trimethoxy-phenyl)-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(3,4-dimethyl-phenyl)-1-methyl-urea,
trans-3-(4-Acetyl-phenyl)-1-{4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-chloro-phenyl)-1-methyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-phenyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-(4-trifluoromethyl-phenyl)-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(3,4-dichloro-phenyl)-1-methyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-bromo-phenyl)-1-methyl-urea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-naphthalen-2-yl-urea,
trans-1-{4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-(4-nitro-phenyl)-urea,

trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-dimethylamino-phenyl)-1-methyl-urea,
trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-1-methyl-3-p-tolyl-urea,
trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-3-(4-fluoro-phenyl)-1-methylurea,
trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-3-(4-bromo-phenyl)-1-methylurea,
trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-3-(4-butyl-phenyl)-1-methylurea,
trans-1-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-1-methyl-3-p-tolyl-urea,
trans-1-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-3-(4-fluoro-phenyl)-1-methylurea,
trans-1-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-3-(4-bromo-phenyl)-1-methylurea,
trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-1-methyl-3-p-tolyl-urea,
trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-3-(4-fluoro-phenyl)-1-methyl-urea,
trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-3-(4-bromo-phenyl)-1-methyl-urea,
trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-3-(4-butyl-phenyl)-1-methyl-urea,
trans-Methyl-{4-[4-(methyl-propyl-amino)-butoxy]-cyclohexyl}-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-N-(4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl)-4-bromo-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-[4-(6-dimethylamino-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-benzenesulfonamide,
trans-N-(4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-4-Bromo-N-[4-(6-diethylamino-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide,
trans-4-Bromo-N-{4-[6-(isopropyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide,

trans-4-Bromo-N-methyl-N-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-benzenesulfonamide,
trans-N-[4-(6-Diethylamino-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[6-(Isopropyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-Methyl-N-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide,
trans-4-Chloro-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-benzenesulfonamide,
trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-4-Chloro-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-benzenesulfonamide,
trans-4-Bromo-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-benzenesulfonamide,
trans-4-Chloro-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-propyl-benzenesulfonamide,
trans-4-Bromo-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-propyl-benzenesulfonamide,
trans-4-Chloro-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-(2,4,5-trifluoro-benzyl)-benzenesulfonamide,
trans-4-Bromo-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-(2,4,5-trifluoro-benzyl)-benzenesulfonamide,
trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid 4-chloro-phenyl ester,
trans-Ethyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid 4-chloro-phenyl ester,
trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-propyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-carbamic acid 4-chloro-phenyl ester,
trans-Ethyl-(4-{6-[ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester,
trans-Benzyl-(4-{6-[ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester,
trans-(4-{6-[Ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid benzyl ester,
trans-Allyl-(4-{6-[ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-carbamic acid

benzyl ester,
trans-(4-{6-[Ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester,
trans-[4-(6-Azetidin-1-yl-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester,
trans-[4-(6-Azetidin-1-yl-hexyloxy)-cyclohexyl]-benzyl-carbamic acid benzyl ester,
trans-[4-(6-Azetidin-1-yl-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester,
trans-Ethyl-(4-{6-[(2-hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester,
trans-Benzyl-(4-{6-[(2-hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester,
trans-(4-{6-[(2-Hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid benzyl ester,
trans-Allyl-(4-{6-[(2-hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester,
trans-(4-{6-[(2-Hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester,
trans-Ethyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester,
trans-Benzyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester,
trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid benzyl ester,
trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester,
trans-Ethyl-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-Benzyl-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-Methyl-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-Allyl-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-[4-(6-Morpholin-4-yl-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester,
trans-Ethyl-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-Benzyl-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-Methyl-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-Allyl-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-[4-(6-Pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid benzyl ester,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-ethyl-carbamic acid benzyl ester,

trans-Allyl-{4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-carbamic acid benzyl ester,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-benzyl-carbamic acid benzyl ester,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester,
trans-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester,
trans-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester,
trans-Allyl-[4-(6-dimethylamino-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-Benzyl-[4-(6-dimethylamino-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester,
trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester,
trans-(4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester,
trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester,
trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester,
trans-4-Chloro-N-ethyl-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-benzenesulfonamide,
trans-4-Bromo-N-ethyl-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-benzenesulfonamide,
trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{6-[Ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,
trans-[4-(4-Dimethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,
trans-[4-(5-Dimethylamino-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,

trans-(4-{6-[Ethyl-(2-methoxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{4-[Ethyl-(2-methoxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{3-[Ethyl-(2-methoxy-ethyl)-amino]-propoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{5-[Ethyl-(2-methoxy-ethyl)-amino]-pentyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-[4-(3-Dimethylamino-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-Methyl-[4-(3-piperidin-1-yl-propoxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester,
trans-Methyl-[4-(4-piperidin-1-yl-butoxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester,
trans-Methyl-[4-(6-piperidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester,
trans-Methyl-[4-(5-piperidin-1-yl-pentyloxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester,
trans-[4-(3-Diethylamino-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,
trans-[4-(6-Diethylamino-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,
trans-[4-(4-Diethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,
trans-[4-(5-Diethylamino-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,
trans-Methyl-[4-(3-pyrrolidin-1-yl-propoxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester,
trans-Methyl-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester,
trans-(4-{6-[(2-Hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{4-[(2-Hydroxy-ethyl)-methyl-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{5-[(2-Hydroxy-ethyl)-methyl-amino]-pentyloxy}-cyclohexyl)-methyl-carbamic

acid 4-chloro-phenyl ester,
trans-Methyl-[4-(4-pyrrolidin-1-yl-butoxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester,
trans-Methyl-[4-(5-pyrrolidin-1-yl-pentyloxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester,
trans-(4-{3-[(2-Hydroxy-ethyl)-methyl-amino]-propoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-[4-(5-Dimethylamino-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester N-oxide,
trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester,
trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-methyl-carbamic acid 4-bromo-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 3,4-difluoro-phenyl ester,
trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-methyl-carbamic acid 3,4-difluoro-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[3-(Allyl-methyl-amino)-propoxymethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-[4-(3-Azetidin-1-yl-propoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,
trans-Methyl-[4-(3-piperidin-1-yl-propoxymethyl)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester,
trans-(4-{3-[Ethyl-(2-methoxy-ethyl)-amino]-propoxymethyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[4-(Allyl-methyl-amino)-butoxymethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[2-(Allyl-methyl-amino)-ethoxymethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-N-{4-[3-(Allyl-methyl-amino)-propoxymethyl]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,

(trans)-N-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(3-Azetidin-1-yl-propoxymethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-Methyl-N-[4-(3-piperidin-1-yl-propoxymethyl)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide,
(trans)-N-[4-(2-Dimethylamino-ethylsulfanylmethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-[4-(2-Diethylamino-ethylsulfanylmethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-{4-[2-(Allyl-methyl-amino)-ethylsulfanylmethyl]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-[4-(2-Diethylamino-ethylsulfanylmethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[2-(Allyl-methyl-amino)-ethylsulfanylmethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[3-(Allyl-methyl-amino)-propylsulfanylmethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-[4-(2-Dimethylamino-ethylsulfanylmethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{2-[Ethyl-(2-hydroxy-ethyl)-amino]-ethylsulfanylmethyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-Methyl-{4-[2-(methyl-propyl-amino)-ethylsulfanylmethyl]-cyclohexyl}-carbamic acid 4-chloro-phenyl ester,
trans-{4-[3-(Allyl-methyl-amino)-prop-1-ynyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-prop-1-ynyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester,
trans-Methyl-{4-[4-(methyl-propyl-amino)-butoxy]-cyclohexyl}-carbamic acid 3,4-difluoro-phenyl ester,
trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-sulfamic acid benzyl amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid phenyl amide,
trans-4-[({4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamoyloxy)-methyl]-benzoic acid methyl ester,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid butyl

amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid phenethyl amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid furan-2-ylmethyl amide,
trans-({4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfonylamino)-acetic acid ethyl ester,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid cyclopropyl amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid 2,2,2-trifluoro-ethyl amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid benzo[1,3]dioxol-5-ylmethyl amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid 4-fluorobenzyl amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-chloro-phenyl)-amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-fluoro-phenyl)-amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-bromo-phenyl)-amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (p-tolyl)-amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (3,4-difluoro-phenyl)-amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-trifluoromethyl-phenyl)-amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (3-fluoro-phenyl)-amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-cyano-phenyl)-amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (2,4-difluoro-phenyl)-amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-methoxy-phenyl)-amide,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (2,5-difluoro-phenyl)-amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid benzyl amide,

trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid phenyl amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-chlorophenyl amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-bromophenyl amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-methylphenyl amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-trifluoromethylphenyl amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-cyanophenyl amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-methoxyphenyl amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid 3,4-difluorophenyl amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid 3-fluorophenyl amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid 2,4-difluorophenyl amide,
trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid 2,5-difluorophenyl amide,
trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-sulfamic acid phenyl amide,
trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-sulfamic acid 3,4-difluorophenyl amide,
trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-sulfamic acid 4-chlorophenyl amide,
trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-sulfamic acid benzyl amide,
trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamic acid phenyl amide,
trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamic acid 3-fluoro phenyl amide,
trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamic acid 3,4-difluoro phenyl amide,
trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamic acid 4-chloro phenyl amide,
trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamic acid benzyl

amide,
trans-({4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamoylamino)-acetic acid ethyl ester,
trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid phenyl amide,
trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid 3-fluoro-phenyl amide,
trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid 3,4-difluoro-phenyl amide,
trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid 4-chloro-phenyl amide,
trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid furan-2-ylmethyl amide,
rans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid benzyl amide,
trans-({4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamoyloxy)-acetic acid ethyl amide,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(2-bromo-4-fluoro-phenyl)-1-methyl-thiourea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-bromo-2-methyl-phenyl)-1-methyl-thiourea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-(4-trifluoromethyl-phenyl)-thiourea,
trans1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-chloro-phenyl)-1-methyl-thiourea,
trans1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-methoxy-phenyl)-1-methyl-thiourea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-cyano-phenyl)-1-methyl-thiourea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-(3-methyl-butyl)-thiourea,
trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-sec-butyl-1-methyl-thiourea,
trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-1-methyl-3-(4-trifluoromethyl-phenyl)-thiourea,
trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-3-(4-cyano-phenyl)-1-methyl-thiourea,
trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-1-methyl-3-(3-methyl-butyl)-thiourea,
trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-1-methyl-3-(4-

trifluoromethyl-phenyl)-thiourea,
trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-3-(4-cyano-phenyl)-1-methyl-thiourea,
trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-1-methyl-3-(3-methyl-butyl)-thiourea,
trans-1-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-1-methyl-3-(4-trifluoromethyl-phenyl)-thiourea,
trans-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-[4-(5-Dimethylamino-pentyloxy)-cyclohexyl]-carbamic acid benzyl ester,
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-carbamic acid benzyl ester,
trans-N-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-N-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide, and
trans-{4-[4-(Allyl-methyl-amino)-butyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
and pharmaceutically acceptable salts thereof.

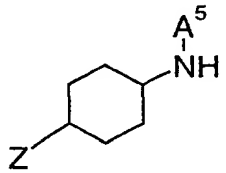
Particularly preferred compounds of general formula (I) are those selected from the group consisting of
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-N-[4-(6-Diethylamino-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[2-(Allyl-methyl-amino)-ethylsulfanylmethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-N-[4-(3-Allylamino-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-methyl-carbamic acid

4-trifluoromethyl-phenyl ester,
trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-methyl-carbamic acid 4-bromo-phenyl ester,
trans-N-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-[4-(4-Dimethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester,
trans-{4-[3-(Allyl-methyl-amino)-prop-1-ynyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-N-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester, and
trans-{4-[4-(Allyl-methyl-amino)-butyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
and pharmaceutically acceptable salts thereof.

Compounds of formula (I) can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers or as racemats. The invention embraces all of these forms.

It will be appreciated, that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

The present invention also relates to a process for the manufacture of compounds as described above, which process comprises reacting a compound of formula (II)



(II)

wherein

A^5 has the significance given above,

Z is a group $(A^1,A^2,)N\text{-}C(A^3,A^4)\text{-}(CH_2)_m\text{-}V\text{-}(CH_2)_n$ or $HO\text{-}(CH_2)_n$, wherein A^1, A^2, A^3,A^4, V, m and n have the significances given above,

with $ClSO_2$-A^6, ClCOO-A^6, ClCSO-A^6, OCN-A^6, SCN-A^6, HOOC-A^6, or $ClSO_2NR^1$-A^6.

The invention further relates to compounds of formula (I) as defined above, when manufactured according to a process as defined above.

As described above, the compounds of formula (I) of the present invention can be used for the treatment and/or prophylaxis of diseases which are associated with OSC such as of hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses and gallstones, and/or treatment and/or prophylaxis of impaired glucose tolerance, diabetes, tumors and/or hyperproliferative disorders.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

Further, the invention relates to compounds as defined above for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, which method comprises administering a compound as defined above to a human being or animal.

The invention further relates to the use of compounds as defined above for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes.

In addition, the invention relates to the use of compounds as defined above for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes. Such medicaments comprise a compound as defined above.

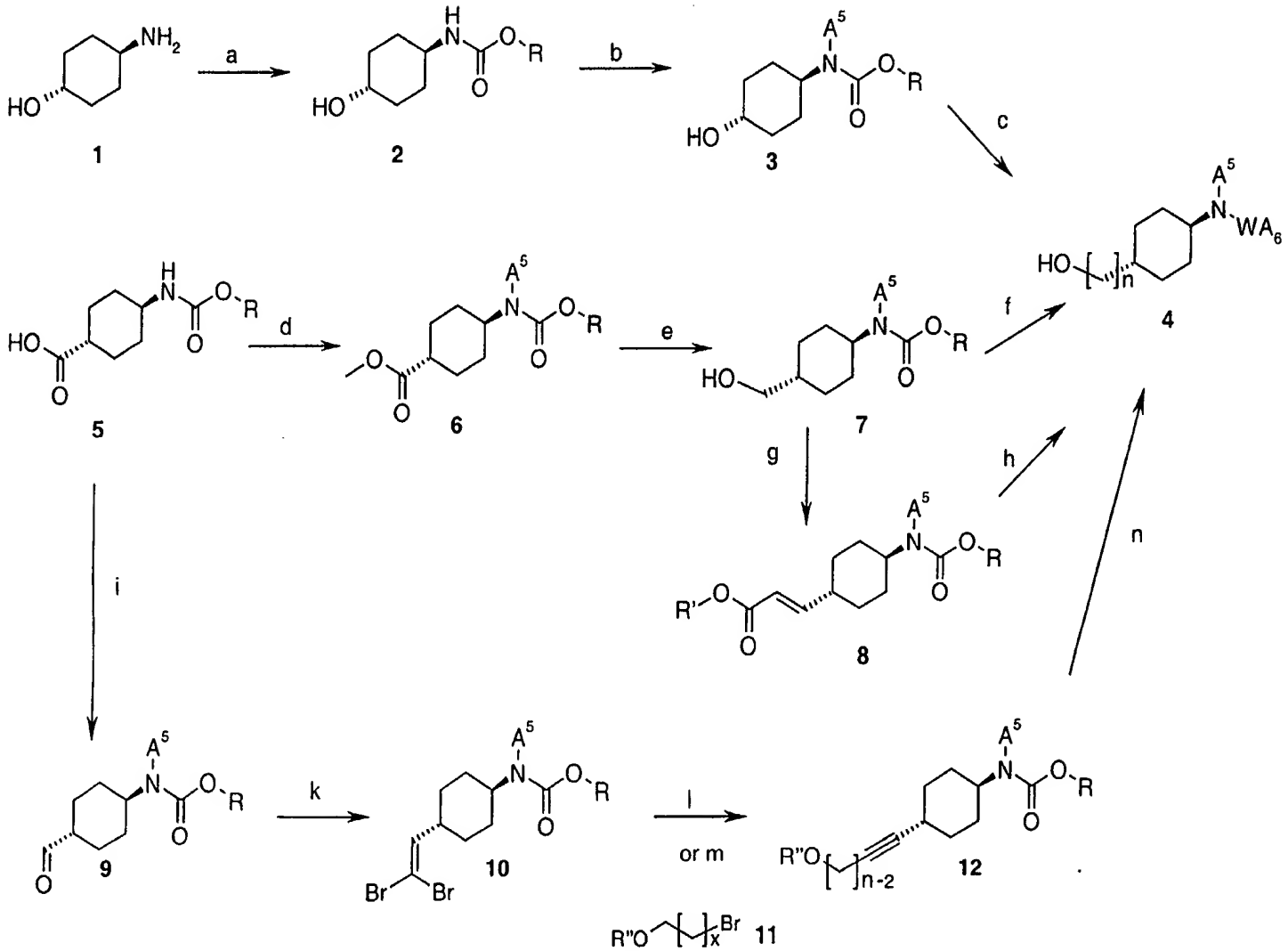
The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to the person skilled in the art. Starting materials are either commercially available or can be prepared by methods analogous to the methods given in the examples or by methods known in the art.

Scheme1

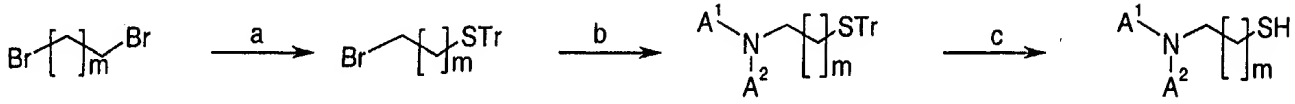
for n=0
R = tBu, Bn

for n=1

for n>=3



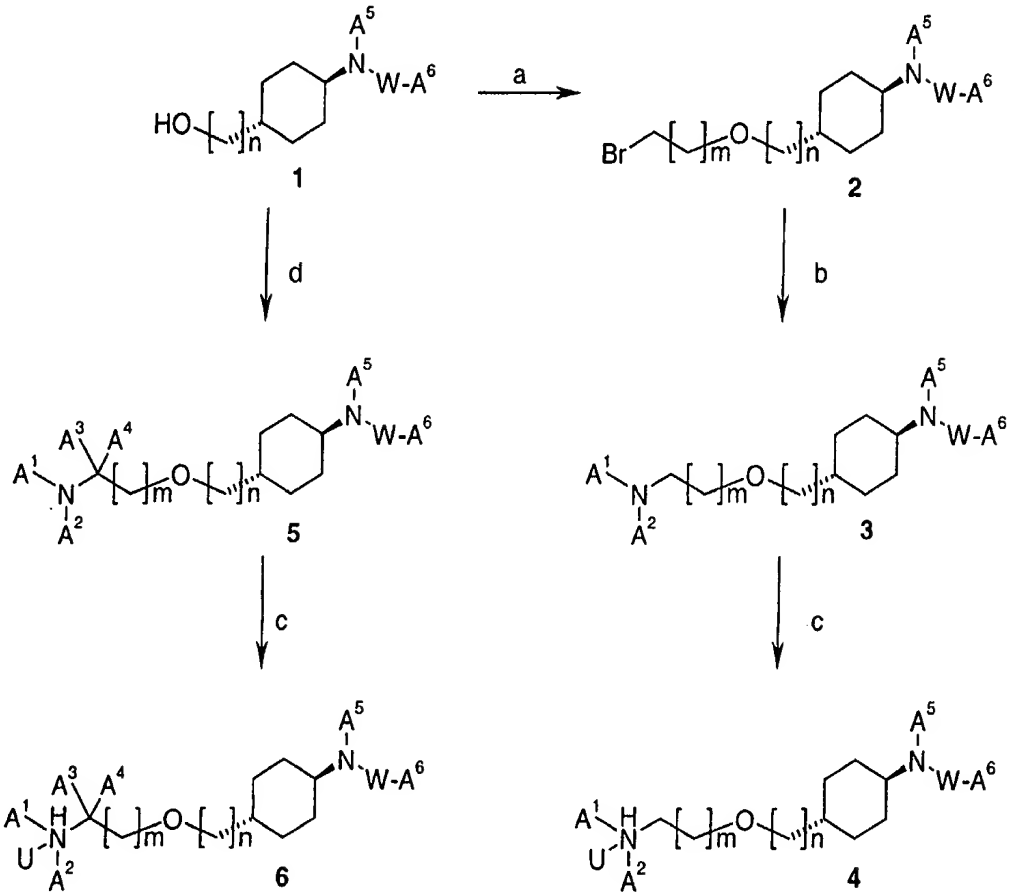
Scheme 2



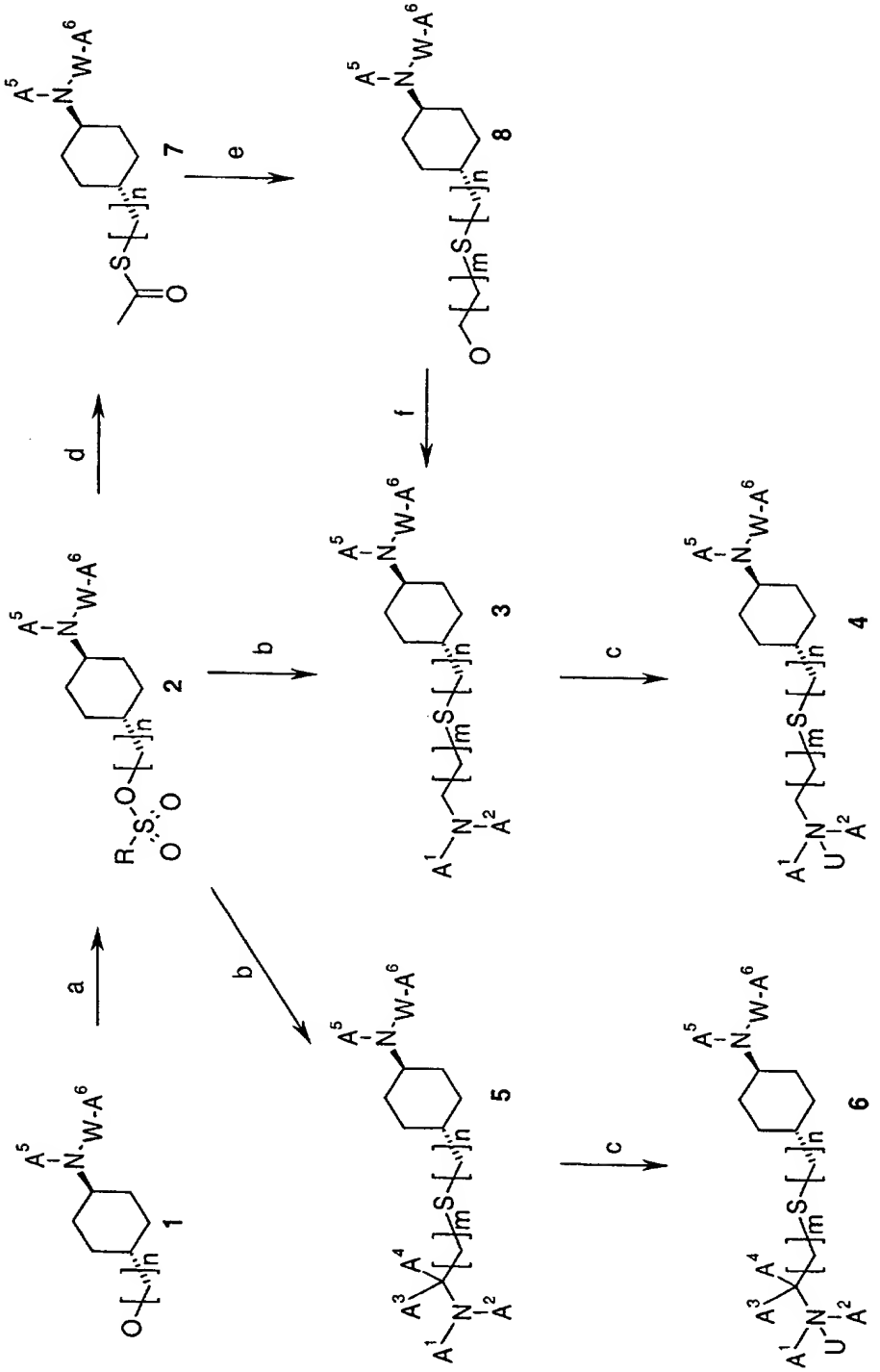
1 2 3 4

Tr= trityl

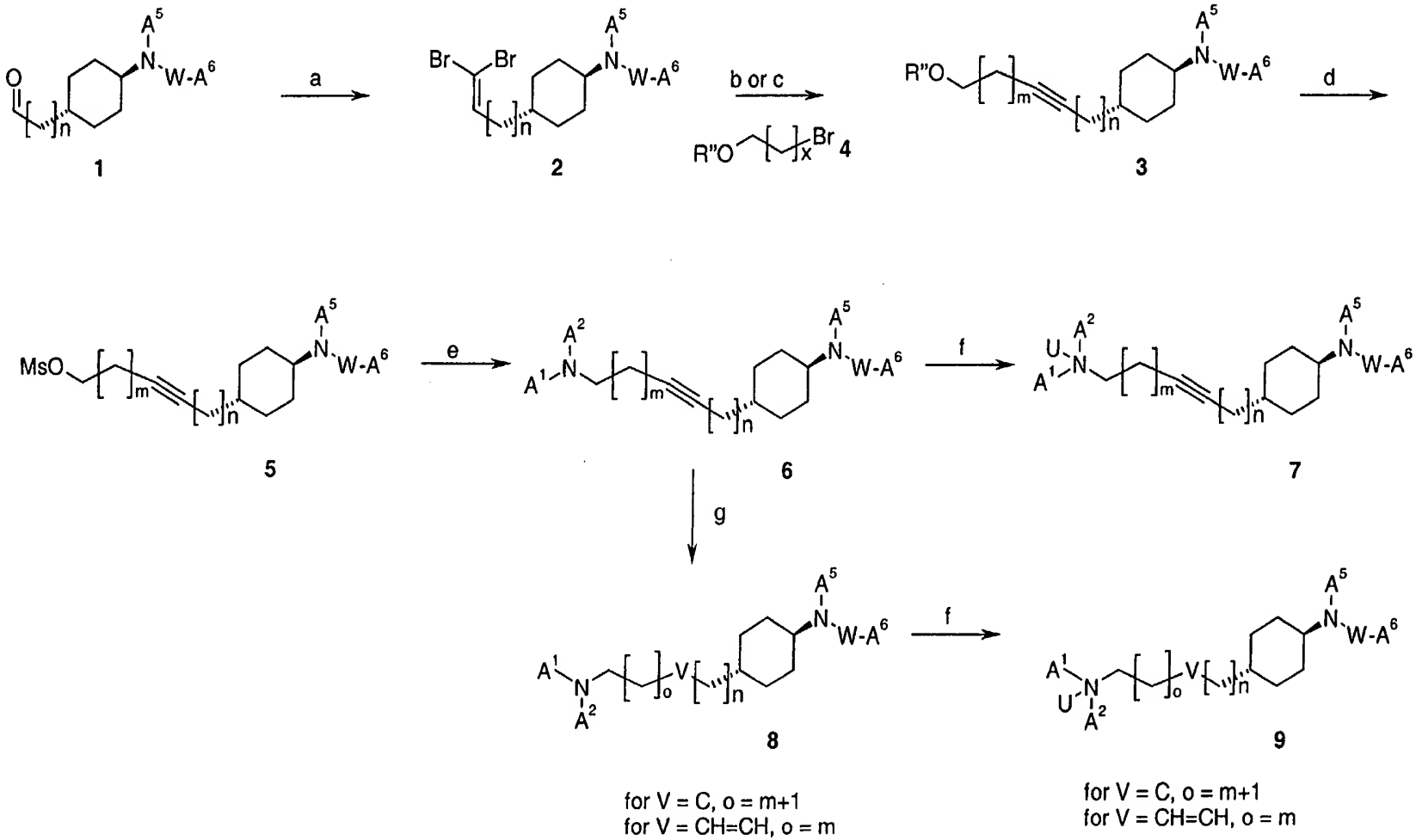
Scheme 3



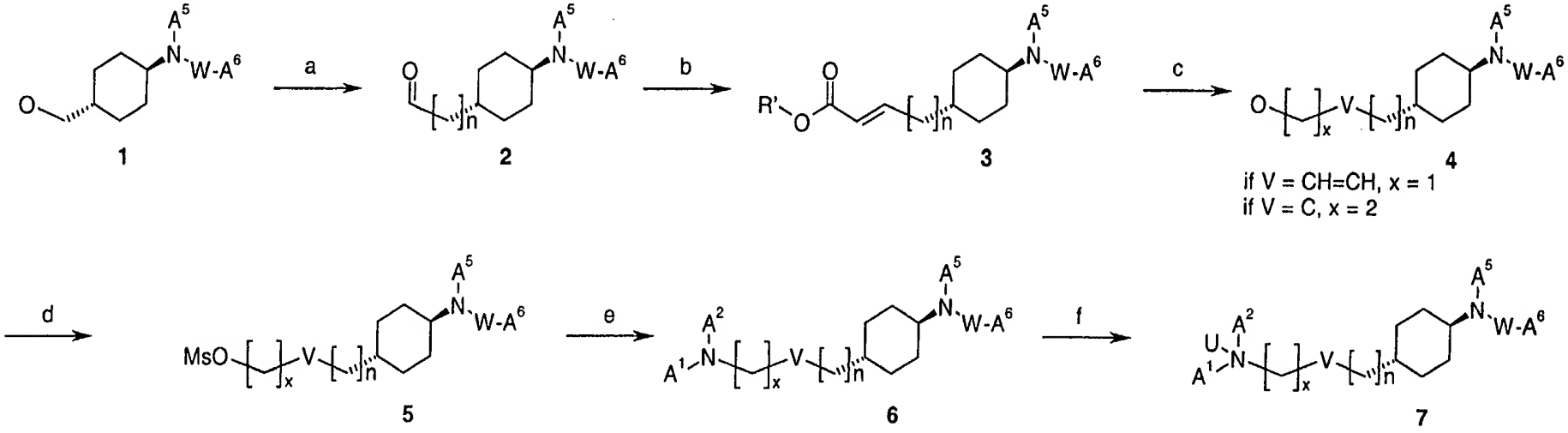
Scheme 4



Scheme 5



Scheme 6



Scheme 1:

The preparation of the starting materials for aminocyclohexyl derivatives of formula (I) in which V is O or S is depicted in scheme 1.

For compounds with n=0, the synthesis starts from trans-4-aminocyclohexanol 1 which is converted to the Z-derivative or the BOC derivative 2 e.g. ZCl, Na_2CO_3, THF, H_2O or $(BOC)_2O$, iPrOH, CH_2Cl_2, respectively (step a). Lithium aluminum hydride reduction yields trans-4-methylaminocyclohexanol which is either BOC-protected to yield compound 3 or is directly transferred into the desired A^6W-derivative 4 using one of the methods described later for compound 3 or 5 in scheme 3. If needed, the aminocyclohexanol derivative can be treated with hexamethyldisilazane at reflux, prior to the introduction of the A^6W-moiety. Alternatively, the residue A^5 can be introduced via alkylation using sodium hydride and a reactive alkyl or arylalkyl derivative (step b). BOC-deprotection (TFA, CH_2Cl_2) or Z–deprotection (hydrogenation) followed by treatment with A^6W-derivatives gives compounds of the formula 4.

For n=1, the starting material is (trans)- 4-tert-butoxycarbonyl amino-cyclohexane-carboxylic acid 5. This is converted to the derivative 6 by ester formation (e.g. carbonyl-di-imidazole, methanol in THF) and direct alkylation using sodium hydride and a reactive alkyl or arylalky derivative (step d). Reduction with lithium aluminum hydride yields the protected alcohol 7.

For n=2, the starting material is trans-4-aminocyclohexyl acetic acid (can be derived from 4-nitrophenylacetic acid according to Karpavichyus, K. I.; Palaima, A. I.; Knunyants, I. L.; BACCAT; Bull.Acad.Sci.USSR Div.Chem.Sci. (Engl.Transl.); EN; 29; 1980; 1689-1694; IASKA6; Izv.Akad.Nauk SSSR Ser.Khim.; RU; 10; 1980; 2374-2379 or T.P. Johnston et al. Journal of Medicinal Chemistry, 1977, Vol, No.2, 279-290.) which can be converted to the corresponding alcohol following the protocol for the compounds 5 to 7.

For n>=3, the starting material is (trans)- 4-tert-butoxycarbonyl amino-cyclohexane-carboxylic acid 5. Chain elongation can be achieved using methods known in the art or as described below:

For C_2-elongation: Swern oxidation of the alcohol 7 to the corresponding aldehyde followed by Horner-Emmons reaction with triethyl phosphono acetate, sodium methanolate in ethanol gave the unsaturated ester 8. This was subjected to hydrogenation with 10% palladium on carbon in methanol and reduction with lithium aluminum hydride in THF to yield the chain-elongated alcohol 4.

For C_2 up to $C_{(n-1)}$-elongation Corey-Fuchs methodology may be used: Therefore, acid 5 is converted to the Weinreb derivative by treatment with N,O-dimethyl-hydroxyl-amine·hydrochloride with EDCI and HOBT in CH_2Cl_2 at room temperature which is reduced by lithium aluminum hydride to the corresponding aldehyde 9 (step i). This aldehyde 9 can be treated with triphenylphosphine, tetrabromomethane and triethylamine in CH_2Cl_2 at 0 °C to RT to yield 2,2-Dibromo-vinyl derivative 10. Rearrangement with n-BuLi (ca 1.6 M in hexane) in THF at -78 °C, followed by reaction with formaldehyde (-78 °C to RT) gives the propargyl alcohol [step l, following conditions described in: Marshall, James A.; Bartley, Gary S.; Wallace, Eli M. Total Synthesis of the Pseudopterane (-)-Kallolide B, the Enantiomer of Natural (+)-Kallolide B. J. Org. Chem. (1996), 61(17), 5729-5735; and Baker, Raymond; Boyes, Alastair L.; Swain, Christopher J. Synthesis of talaromycins A, B, C, and E. J. Chem. Soc., Perkin Trans. 1 (1990), (5), 1415-21.], from which the propanol derivative 4 can be obtained by hydrogenation with 10%Pd/C.

For longer side chains, the rearrangement is performed with n-BuLi (ca 1.6 M in hexane) in THF at -78 °C as above, followed by addition of a cosolvens such as DMPU and reaction with O-protected 1-bromo-alcohols 11 (step m; e.g. 1-bromo-n-tetrahydropyaranyloxyalkane) to give the O-protected compounds 12. 12 can be converted to the alkanol derivatives by hydrogenation with 10%Pd/C followed by deprotection to yield the derivatives 4.

If WA^6 is a protective group, this may be cleaved as described for derivative 3 and the final moieties WA^6 may be introduced as described for the compounds in scheme 3.

Scheme 2:

Scheme 2 shows the synthesis of aminothiols 4 that are used for the synthesis of compounds with thioether spacers. Triphenylmethanethiol is deprotonated with NaH in DMA and reacted with α,ω-dihaloalkane in DMA (step a). Treatment with the amine A^1A^2NH yields the S-protected amine 3 (step b). Deprotection of the thiol moiety may be achieved by treatment with TFA/triisopropylsilane in CH_2Cl_2 at 0 °C to RT to give the aminothiol 4 (step c).

Scheme 3:

The synthesis of ether derivatives of formula (I) is depicted in scheme 3. For the preparation of derivatives with n=0, the aminocyclohexanol derivative 1 can be treated under phase transfer conditions e.g. α,ω -dihaloalkanes, NaOH, nBu_4NHSO_4 to yield

bromide 2. For n>0, alcohol derivative 1 may be treated with α,ω-dihaloalkane (for C_4 or longer alkanes) in the presence of NaH in DMF 0 °C to RT to yield bromide 2. For shorter alkanes the method of choice is the in situ generation of the haloalkane-triflate (from the corresponding haloalkanol with trifluoromethansulfonic anhydride/2,6-di-tert-butylpyridine in CH_2Cl_2 at 0 °C). This haloalkane-triflate is then reacted with alcohol 1 with 2,6-di-tert-butylpyridine as base in nitromethane at 60 °C to yield bromide 2 [following a procedure of Belostotskii, Anatoly M.; Hassner, Alfred. Synthetic methods. 41. Etherification of hydroxysteroids via triflates. Tetrahedron Lett. (1994), 35(28), 5075-6].

Amination of bromide 2 with amine A^1A^2NH in DMA or DMF, at RT yields the final amine 3, optionally DBU may be added. Amine 3 may be converted to a salt or to the N-oxide 4 using a mixture of hydrogen peroxide urea adduct and phthalic anhydride in CH_2Cl_2 at RT.

Alternatively, the alcohol 1 can be converted to the amine 5 by attaching the pre-assembled fragment $A^1A^2NC(A^3A^4)(CH_2)_m$-OH, which can be synthesized by known methods, to the mesylate/halogenide of derivative 1using alkylating conditions (step d). The amine 5 can be converted to its salt or the N-oxide 6 as described above (step c).

If A^6W is a protecting moiety this can be cleaved prior to salt or n-oxide formation using TFA in CH_2Cl_2 for BOC-groups or by hydrogenation in methanol with Pd/C for Z–groups. The resulting amine (not shown) may be treated according to one of the following procedures to derive the appropriate A^6W derivative 3 or 5.

a) Sulfonamides: Sulfonylation of the amines is done in dioxane or CH_2Cl_2 with Huenig's base and a sulfonyl chloride over night at RT to yield the sulfonamide 3 or 5.

b) Carbamates: The amines may be reacted with A^6OCOCl/Huenig's base in dioxane or CH_2Cl_2. Alternatively, the chloroformates may be prepared in situ by treatment of A^6OH with Cl_3COCl in the presence of quinoline followed by reaction with the amines in the presence of Huenig's base.

c) Thiocarbamates: The amines may be reacted with A^6OCSCl in dioxane.

d) Ureas: The amines may be reacted with isocyanate in dioxane at room temperature.

e) Thioureas: The amines may be reacted with isothiocyanate in dioxane at room temperature.

f) Amides: The amines may be reacted with A^6COOH/EDCI/DMAP (with anhydride formation, and subsequent addition of the starting amine at - 10 °C to room temperature) or alternatively with A^6COOH/EDCI/DMAP or A^6COOH/Huenig's base/EDCI/HOBT in DMF, dioxane or CH_2Cl_2 at room temperature.

g) Sulfamides: The amines may be reacted with sulfamoyl chlorides in dioxane in the presence of an excess of triethylamine to yield sulfamide 3 or 5. The sulfamoyl chlorides can be prepared from A^6NH_2 and chlorosulfonic acid in CH_2Cl_2 at 0 °C to room temperature followed by reaction with PCl_5 in toluene at 75 °C. Alternatively, the sulfamoyl chlorides can be synthesized in acetonitrile with A^6NH_2 and sulfuryl chloride at 0 °C to 65 °C.

Scheme 4:

Scheme 4 shows the synthesis of thio ether derivatives of formula I in which V is S. For compounds in which n is 0, mesylation is performed under inversion (Mitsunobu conditions, step a). For compounds with n>0, the alcohol 1 can be mesylated with methanesulfonyl chloride in pyridine in the presence of DMAP at 0 °C to RT to yield sulfonate 2 (step a). Sulfonate 2 is then thiolated with the corresponding A^1A^2aminoalkanethiol (in analogy to the methods described in context with scheme 2) with NaH as base in DMF at 0 °C to RT to give the final compound 3 or 5, respectively (step b).

Another approach for the synthesis of thioether 3, which opens up the possibility to vary the A1A2amine terminus at the end, is depicted in steps d - f. Sulfonate 2 is treated with potassium thioacetate in DMF at 100 °C to yield thioacetate 7. Deprotection with 1N LiOH in ethanol and alkylation with haloalkanol gives alcohol 8. The alcohol 8 is treated with methanesulfonyl chloride in pyridine in the presence of DMAP at 0 °C to RT to yield the mesylate/chloride which can be aminated with the corresponding A^1A^2amine in the presence of NaI in DMA to yield the final amine 3. If WA^6 is a protecting group this can be cleaved and the resulting amine can be converted to the desired WA^6 derivative by employing one of the methods described for compounds 3 and 5 in scheme 3.

The amines 3or 5 can optionally be converted to a salt or to the N-oxide 4 or 6 (step c, with e.g. hydrogen peroxide urea adduct and phthalic anhydride in CH_2Cl_2 at RT).

Scheme 5:

In scheme 5 the synthesis of C-analogues aminocyclohexanes of the general structure I in which V is $-CH_2-$, -CH=CH- or -C≡C- is described. The synthesis starts from aldehyde 1 which can be derived from (trans)- 4-tert-butoxycarbonyl amino-cyclohexane-carboxylic acid (see scheme 1, compound 9) or from the corresponding alcohol (compound 4, scheme 1) by Swern oxidation. Side chain extension is effected through application of the Corey-Fuchs method. The aldehyde 1 is treated with triphenylphosphine, tetra-bromo-methane and triethylamine in CH_2Cl_2 at 0 °C to RT to yield 2,2-Dibromo-vinyl derivative 2. Rearrangement with n-BuLi (ca 1.6 M in hexane) in THF at -78 °C, followed by reaction with formaldehyde (-78 °C to RT) leads to the propargyl alcohol 3 [following conditions described in: Marshall, James A.; Bartley, Gary S.; Wallace, Eli M. Total Synthesis of the Pseudopterane (-)-Kallolide B, the Enantiomer of Natural (+)-Kallolide B. J. Org. Chem. (1996), 61(17), 5729-5735; and Baker, Raymond; Boyes, Alastair L.; Swain, Christopher J. Synthesis of talaromycins A, B, C, and E. J. Chem. Soc., Perkin Trans. 1 (1990), (5), 1415-21.].

For longer side chains, the rearrangement is performed with n-BuLi (ca 1.6 M in hexane) in THF at -78 °C as above, followed by addition of a cosolvens such as DMPU and reaction with O-protected 1-bromo-alcohols 4 (e.g. 1-bromo-n-tetrahydro-pyaranyloxyalkane) to yield the O-protected compounds 3 which can be by deprotected to the corresponding alkinol derivative (in MeOH at 50-60 °C in the presence of catalytic amount of pyridinium toluene-4-sulfonate).

Mesylation of alcohol 3 with methanesulfonylchloride, pyridine and DMAP in CH_2Cl_2 at 0 °C to RT yields mesylate 5 which can be converted to the amine 6 in DMA at RT with an excess of the corresponding amine NHA^1A^2 (step e).

If A^6W is a protecting moiety this can be cleaved prior to salt or n-oxide formation using TFA in CH_2Cl_2 for BOC-groups or by hydrogenation in methanol with Pd/C for Z–groups. The resulting amine (not shown) may be treated according to one of the procedures described for scheme 3 to yield the appropriate A^6W derivative 6.

Optionally the introduction of the desired A^6W moiety can be performed at an earlier stage, e.g. derivative 2 or O-protected derivative 3 or mesylated compound 5 to enable an optimization of the NA^1A^2 terminus.

Compounds in which V is $-CH_2-$ or -CH=CH- can be obtained by hydrogenation of compound 6 with Pt/C (yields the saturated analogue 8) or by hydrogenation with other known methods (yields the double bond analogue 8).

The amines 6 and 8 can be converted to a salt or as described in step f to the N-oxide 7 and 9, respectively, using a mixture of hydrogen peroxide urea adduct and phthalic anhydride in CH_2Cl_2 at RT.

Scheme 6:

The synthesis of C-analogues in which V is $-CH_2-$ or -CH=CH- is depicted in scheme 6. Alcohol 1 can be transformed to the aldehyde 2 via Swern-oxidation. Alternatevely, alcohol 1 can be tosylated (tosylchloride in pyridine) followed by treatment with NaCN (in DMF at 100 °C) and redudtion with DIBALH (–78 °C to RT in THF) to give the C1-elongated aldyhyde 2. Horner-Emmons reaction with triethyl phosphono acetate, sodium methanolate in ethanol yields the unsaturated ester 3 (step b). Ester 3 can either be reduced directly to the unsaturated alcohol 4 (V is -CH=CH-, x=1) or can be hydrogenated with 10% Pd/C in methanol and reduced with lithium aluminum hydride in THF to the saturated alcohol 4 (V is $-CH_2-$, x=2). The alcohol is mesylated with methane sulfonyl chloride, triethylamine in CH_2Cl_2 to yield mesylate 5 (step d) which is treated with the desired amine A^1A^2NH to yield the derivative 6 (step e). As described for the previous schemes, for the cases A^6W is a protecting group (BOC or Z), this can be cleaved and the appropriate A^6W moiety introduced using the methods shown in scheme 3.

The amines 6 can be converted to a salt or, as described in step f, to the N-oxide 7 using a mixture of hydrogen peroxide urea adduct and phthalic anhydride in CH_2Cl_2 at RT.

The following tests were carried out in order to determine the activity of the compounds of formula I and their salts.

Inhibition of human liver microsomal 2,3-oxidosqualene-lanosterol cyclase (OSC)

Liver microsomes from a healthy volunteer were prepared in sodium phosphate buffer (pH 7.4). The OSC activity was measured in the same buffer, which also contained 1mM EDTA and 1mM dithiothreitol. The microsomes were diluted to 0.8mg/ml protein in cold phosphate buffer. Dry [^{14}C]R,S-monooxidosqualene (MOS, 12.8 mCi/mmol) was diluted to 20 nCi/µl with ethanol and mixed with phosphate buffer-1% BSA (bovine serum albumin). A stock solution of 1 mM test substance in DMSO was diluted to the desired concentration with phosphate buffer-1% BSA. 40 µl of microsomes were mixed with 20 µl of the solution of the test substance and the reaction was subsequently started with 20 µl of the [^{14}C]R,S-MOS solution. The final conditions were: 0.4mg/ml of microsomal proteins and 30 µl of [^{14}C]R,S-MOS in phosphate buffer, pH 7.4, containing 0.5% albumin, DMSO <0.1% and ethanol <2%, in a total volume of 80 µl.

After 1 hour at 37°C the reaction was stopped by the addition of 0.6 ml of 10% KOH-methanol, 0.7ml of water and 0.1ml of hexane:ether (1:1, v/v) which contained 25 µg of non-radioactive MOS and 25 µg of lanosterol as carriers. After shaking, 1 ml of hexane:ether (1:1, v/v) was added to each test tube, these were again shaken and then centrifuged. The upper phase was transferred into a glass test tube, the lower phase was again extracted with hexane:ether and combined with the first extract. The entire extract was evaporated to dryness with nitrogen, the residue was suspended in 50 µl of hexane:ether and applied to a silica gel plate. Chromatographic separation was effected in hexane:ether (1:1, v/v) as the eluent. The Rf values for the MOS substrate and the lanosterol product were 0.91 and, respectively, 0.54. After drying, radioactive MOS and lanosterol were observed on the silica gel plate. The ratio of MOS to lanosterol was determined from the radioactive bands in order to determine the yield of the reaction and OSC inhibition.

The test was carried out on the one hand with a constant test substance concentration of 100nM and the percentage OSC inhibition against controls was calculated. The more preferred compounds of the present invention exhibit inhibitions larger than 50%. In addition, the test was carried out with different test substance concentrations and subsequently the IC_{50} value was calculated, i.e. the concentration required to reduce the conversion of MOS into lanosterol to 50% of the control value. The preferred compounds of the present invention exhibit IC_{50} values of 1 nM to 10 µM, preferrably of 1 - 100 nM.

The compounds of formula I and their pharmaceutically acceptable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula I can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 mg to about 1000 mg, especially about 50 mg to about 500 mg, comes into consideration for the prevention and

control of topical and systemic infections by pathogenic fungi. For cholesterol lowering and treatment of impaired glucose tolerance and diabetes the daily dosage conveniently amounts to between 1 and 1000mg, preferably 10 to 100mg, for adult patients. Depending on the dosage it is convenient to administer the daily dosage in several dosage units.

The pharmaceutical preparations conveniently contain about 1-500 mg, preferably 10-100 mg, of a compound of formula I.

The following Examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

Abbreviations:

AcOH = acetic acid, EtOAc = ethylacetate, EtOH = ethanol, THF = tetrahydrofurane, Et_2O = diethylether, MeOH = methanol, CH_2Cl_2 = dichloromethane, BOC = t-butyloxycarbonyl, BuLi = Butyllithium, DEAD = Diethyl azodicarboxylate, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene(1,5-5), DMAP = 4-Dimethylaminopyridine, DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone, DIBALH = Di-*i*-butylaluminium hydride, EDCI = N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride, Et_3N = triethylamine, HOBT = 1-Hydroxybenzo-triazole, LAH = Lithium aluminium hydride, $LiBH_4$ = lithium borohydride, LDA = lithium diisopropylamide, NaI = sodium iodide, $PdCl_2(dppf)$ = (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II).CH_2Cl_2 (1:1), $Pd(Ph_3P)_4$ = tetrakis(triphenylphosphine)palladium, Huenig's base = iPr_2NEt = N-ethyldiiso-propylamine, TBDMSCl = t-butyldimethylsilyl chloride, TFA = trifluoroacetic acid.

General remarks

All reactions were performed under argon.

The purification of the final amines by preparative HPLC [e.g. RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile] yielded mixtures of the corresponding amino formate and the corresponding halogenide which was used in the reaction. The ratio was not always determined, the purity the final amino salts was >80% after LC-MS.

Example 1

1.1

To a suspension of 50 g (0.33 mol) trans-4-aminocyclohexanol·hydrochloride and 77 g (0.726 mol, 2.2 eq) Na_2CO_3 in 650 ml THF and 150 ml water, 51.2 ml (0.363 mol, 1.1 eq) benzyl chloroformate were added at 5°C over a period of 20 min. The reaction mixture was stirred at RT for 2h, diluted with EtOAc and the phases were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated. Trituration from hexane yielded 162.4 g (98%) trans-4-Hydroxy-cyclohexylcarbamic acid benzyl ester as white crystals, MS: 249 (M) (in analogy to: Venuti, Michael C.; Jones, Gordon H.; Alvarez, Robert; Bruno, John J.; J.Med.Chem.; 30; 2; 1987; 303-318).

1.2

To a suspension of 37.9 g (0.94 mol, 2.0 eq) LAH in 1.3 l THF was added a suspension of 117 g (0.47 mol) trans-4-Hydroxy-cyclohexylcarbamic acid benzyl ester in 1 l THF over a period of 6h via a cannula keeping the temperature between 5-10°C. The reaction was refluxed over night and a mixture of Na_2SO_4, silica gel and water (160g, 50g, 80 ml) was added, stirred for additional 30 min, filtered and concentrated. The crude material was titurated with hexane to yield 27.9 g (46%) trans-4-Methylamino-cyclohexanol. Column chromatography of the mother liquor on silica gel yielded additional 17.1 g (28%) trans-4-Methylamino-cyclohexanol as white solid, MS: 129 (MH^+) (in analogy to Venuti, Michael C.; Jones, Gordon H.; Alvarez, Robert; Bruno, John J.; J.Med.Chem.; 30; 2; 1987; 303-318).

1.3

13.32 g (103 mmol) trans-4-Methylamino-cyclohexanol were dissolved in isopropanol and treated with 24.75 g (113.4 mmol) di-tert-butyl-dicarbonate in CH_2Cl_2. The reaction mixture was stirred at RT over night, concentrated to yield 23.3 g (98%) trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid tert-butyl ester as white solid, MS: 229 (M^+).

1.4

To a suspension of 2.0 g (8.7 mmol) trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid tert-butyl ester in 56.5 ml (261 mmol, 30 eq) 1,4-Dibromobutane, 0.89g (2.6 mmol, 0.3 eq) tetrabutylammoniumhydrogensulfate and 56 ml 50% aqueous NaOH were added. The mixture was stirred at RT for 4 days, CH_2Cl_2 was added and the layers were separated. The inorganic layer was extracted with CH_2Cl_2, the combined organic layers washed with brine and dried over Na_2SO_4. The excess of dibromide was removed in vacuo and the residue was purified by column chromatography on silica gel with hexane:EtOAc 4:1 as eluent

yielding 2.4 g (76%) trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid tert-butyl ester as light yellow oil, MS: 364 (MH^+, 1Br).

1.5

To 1.7 g (4.7 mmol) trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid tert-butyl ester in 22 ml DMA, 1.34 ml (14 mmol, 3 eq) N-allylmethylamine were added over a period of 10 min. The reaction was stirred at RT over night, concentrated and the residue was dissolved in CH_2Cl_2/ 5% aqueous $NaHCO_3$. The phases were separated and the inorganic phase was extracted with CH_2Cl_2, the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated to yield 1.5 g (92%) trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester as colorless oil, MS: 355 (MH^+).

1.6

In analogy to examples 1.4 and 1.5, trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid tert-butyl ester was reacted with 1,3-dibromopropane to yield trans-[4-(3-Bromo-propoxy)-cyclohexyl]-methyl-carbamic acid tert-butyl ester which was reacted with N-allylmethylamine to yield trans-(4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester as colorless oil, MS: 341 (MH^+).

1.7

In analogy to examples 1.4 and 1.5, trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid tert-butyl ester was reacted with 1,5-dibromopentane to yield trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-methyl-carbamic acid tert-butyl ester which was reacted with N-allylmethylamine to yield trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester as white oil, MS: 369 (MH^+).

1.8

In analogy to examples 1.4 and 1.5, trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid tert-butyl ester was reacted with 1,6-dibromohexane to yield trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid tert-butyl ester which was reacted with N-allylmethylamine to yield trans-(4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester as light brown oil, MS: 382 (M).

1.9

In analogy to examples 1.4 and 1.5, trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid tert-butyl ester was reacted with 1,7-dibromoheptane to yield trans-[4-(7-Bromo-heptyloxy)-cyclohexyl]-methyl-carbamic acid tert-butyl ester which was reacted with N-

allylmethylamine to yield trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester as colorless oil, MS: 397 (MH^+).

1.10

2.1 g (5.9 mmol) trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester in 28 ml CH_2Cl_2 were treated with 6 ml TFA at 0°C for 1h, the mixture was concentrated in vacuo and dissolved in EtOAc and saturated aqueous $NaHCO_3$ solution. The phases were separated and the inorganic phase was extracted with EtOAc, the combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated to yield 1.38 g (91%) trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine as yellow oil, MS: 255 (MH^+).

1.11

In analogy to example 1.10, trans-(4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester was converted to yield trans-(4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl)-methyl-amine as yellow oil, MS: 241 (MH^+).

1.12

In analogy to example 1.10, trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester was converted to yield trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine as yellow oil, MS: 269 (MH^+).

1.13

In analogy to example 1.10, trans-(4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester was converted to yield trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine as yellow oil, MS: 283 (MH^+).

1.14

In analogy to example 1.10, trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-carbamic acid tert-butyl ester was converted to yield trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine as colorless oil, MS: 297 (MH^+).

Example 2

A solution of 0.153 mmol of free amine in 0.35 ml dry dioxane was treated with 0.23 mmol isocyanate in 0.54 ml dry dioxane. The solution was allowed to stand over night at room temperature. The resulting reaction mixture was treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation the urea was obtained as amino formate. The following compounds were prepared from the corresponding amines and isocyanates:

Example	Compound	MS MH^+	Amine	Isocyanate
2.1	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(2,4-difluoro-phenyl)-1-methyl-urea	438	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2,4-Difluoro-phenylisocyanate
2.2	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(2,4-dimethoxy-phenyl)-1-methyl-urea	462	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2,4 Dimethoxy-phenylisocyanate
2.3	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-fluoro-phenyl)-1-methyl-urea	420	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Fluorophenyl-isocyanate
2.4	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-methoxy-phenyl)-1-methyl-urea	432	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Methoxy-phenylisocyanate

2.5	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-p-tolyl-urea	416	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Methylphenyl-isocyanate
2.6	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-methoxy-2-methyl-phenyl)-1-methyl-urea	446	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Methoxy-2-Methylphenyl-isocyanate
2.7	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(2,4-dimethyl-phenyl)-1-methyl-urea	430	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2,4 Dimethyl-phenylisocyanate
2.8	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-(3,4,5-trimethoxy-phenyl)-urea	492	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3,4,5 Trimethoxy-phenylisocyanate
2.9	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(3,4-dimethyl-phenyl)-1-methyl-urea	430	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3,4 Dimethyl-phenylisocyanate
2.10	trans-3-(4-Acetyl-phenyl)-1-{4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-urea	444	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Acetylphenyl-isocyanate
2.11	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-chloro-phenyl)-1-methyl-urea	436 (1 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Chlorphenyl-isocyanate

2.12	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-phenyl-urea	402	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Phenylisocyanate
2.13	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-(4-trifluoromethyl-phenyl)-urea	470	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Trifluoro-methylisocyanate
2.14	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(3,4-dichloro-phenyl)-1-methyl-urea	470 (2 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3,4 Dichloro-phenylisocyanate
2.15	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-bromo-phenyl)-1-methyl-urea	480 (1 Br)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Bromphenyl-isocyanate
2.16	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-naphthalen-2-yl-urea	452	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2-Naphthyl-isocyanate
2.17	trans-1-{4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-(4-nitro-phenyl)-urea	447	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Nitrophenyl-isocyanate
2.18	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-dimethylamino-phenyl)-1-methyl-urea	445	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Dimethyl-aminophenyl-isocyanate

2.19	trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-1-methyl-3-p-tolyl-urea	430	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	4-Toloyl-isocanate
2.20	trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-3-(4-fluoro-phenyl)-1-methylurea	434	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	4-Fluorophenyl-isocyanate
2.21	trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-3-(4-bromo-phenyl)-1-methylurea	494 (1 Br)	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	4-Bromophenyl-isocyanate
2.22	trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-3-(4-butyl-phenyl)-1-methylurea	472	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	4-Butylphenyl-isocyanate
2.23	trans-1-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-1-methyl-3-p-tolyl-urea	402	trans-(4-[7-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Toloyl-isocanate
2.24	trans-1-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-3-(4-fluoro-phenyl)-1-methylurea	406	trans-(4-[7-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Fluorophenyl-isocyanate
2.25	trans-1-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-3-(4-bromo-phenyl)-1-methylurea	466 (1 Br)	trans-(4-[7-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Bromophenyl-isocyanate

2.26	trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-1-methyl-3-p-tolyl-urea	388	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-Toloyl-isocanate
2.27	trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-3-(4-fluoro-phenyl)-1-methyl-urea	392	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-Fluorophenyl-isocyanate
2.28	trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-3-(4-bromo-phenyl)-1-methyl-urea	452 (1 Br)	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-Bromophenyl-isocyanate
2.29	trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-3-(4-butyl-phenyl)-1-methyl-urea	430	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-Butylphenyl-isocyanate

Example 3

A solution of 0.153 mmol of amine in 0.35 ml dry dioxane was treated with (2 equivalents or 4 equivalents if the amine·dihydrochloride was used) Huenig's base and 0.2 mmol chloroformate in 0.54 ml dry dioxane. The solution was allowed to stand over night at room temperature and the resulting reaction mixture was treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation the carbamate was obtained as a mixture of amino hydrochloride and formate. The following compounds were prepared from the corresponding amines and chloroformates:

Example	Compound	MS MH^+	Amine	Chloroformate
3.1	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-nitro-phenyl ester	448	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Nitrophenyl-chloroformate
3.2	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid naphthalen-2-yl ester	453	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2-Napthyl-chloroformate
3.3	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid pentafluorophenylmethyl ester	507	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Pentafluorobenzyl chloroformate
3.4	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid benzyl ester	417	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Benzyl-chloroformate

3.5	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid phenyl ester	403	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Phenyl-chloroformate
3.6	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid p-tolyl ester	417	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	p-Tolyl-chloroformate
3.7	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester	481 (1 Br)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Bromophenyl-chloroformate
3.8	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-fluoro-phenyl ester	421	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Fluorophenyl-chloroformate
3.9	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester	437 (1 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Chlorophenyl-chloroformate
3.10	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid hexyl ester	411	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Hexyl-chloroformate
3.11	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-methoxy-phenyl ester	433	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Methoxy-phenyl-chloroformate

3.12	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid isobutyl ester	383	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Isobutyl-chloroformate
3.13	trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester	495 (1 Br)	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	4-Bromophenyl-chloroformate
3.14	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester	467 (1 Br)	trans-(4-[7-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Bromophenyl-chloroformate
3.15	trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester	453 (1 Br)	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-Bromophenyl-chloroformate
3.16	trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-carbamic acid 4-fluoro-phenyl ester	435	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	4-Fluorophenyl-chloroformate
3.17	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-carbamic acid 4-fluoro-phenyl ester	407	trans-(4-[7-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Fluorophenyl-chloroformate
3.18	{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester	409 (1 Cl)	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-chloro-phenyl chloroformate

3.19	{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid isobutyl ester	355	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	isobutyl chloroformate
3.20	{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid phenyl ester	375	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	phenyl chloroformate
3.21	4-({4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamoyloxy)-benzoic acid methyl ester	433	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-methoxy-carbonyl-phenyl chloroformate
3.22	{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-methoxy-phenyl ester	405	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-methoxy-phenyl chloroformate
3.23	{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid p-tolyl ester	389	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	p-tolyl chloroformate
3.24	{ 4-trans-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-carbamic acid 4-fluoro-phenyl ester	379	trans-(4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl)-methyl-amine	4-fluoro-phenyl chloroformate
3.25	{ 4-trans-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester	439 (1 Br)	trans-(4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl)-methyl-amine	4-bromo-phenyl chloroformate

Example 4

A solution of 1.5 mmol trichloromethyl-chloroformate (diphosgene) in 20 ml CH_2Cl_2 was treated at 0 °C with 3 mmol of a suitable substituted phenol and 3 mmol quinoline and then stirred for 3 h at room temperature. The reaction was then cooled (0 °C) and a solution of 1 mmol amine and 2.5 mmol pyridine in 3 ml CH_2Cl_2 was added, followed by 1 mmol DMAP. The mixture was stirred over night at room temperature, treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation the carbamate was obtained as a mixture of amino hydrochloride and formate. The following compounds were prepared from the corresponding amines and chloroformates:

Example	Product	MS MH^+	Amine	In situ generated Chloroformate
4.1	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	471	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Trifluoro-methyl-phenyl-chloroformate
4.2	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	457	trans-(4-[7-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Trifluoro-phenyl-chloroformate
4.3	trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	443	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-trifluoro-methyl-phenyl chloroformate
4.4	trans{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 2,4-difluoro-phenyl ester	439	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2,4-difluoro-phenyl chloroformate

Example 5

A solution of 0.143 mmol amine in 0.35 ml dry dioxane was treated with (0.46mmol; 3 equivalents) Huenig's base and 0.18 mmol sulfonylchloride in 0.5 ml dry dioxane. The solution was allowed to stand over night at room temperature. The resulting reaction mixture was treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation, the sulfonamide was obtained as a mixture of amino hydrochloride and formate. The following compounds were prepared from the corresponding amines and sulfonylchlorides:

Example	Compound	MS MH^+	Amine	Sulfonylchloride
5.1	trans-5-Chloro-thiophene-2-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	463 (1 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	5-Chloro-thiophene-2-sulphonylchloride
5.2	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4,N-dimethyl-benzenesulfonamide	437	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Tosylsulphonyl-chloride
5.3	trans-Naphthalene-2-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	473	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2-Naphthyl-sulphonylchloride
5.4	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-methanesulfonamide	361	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Methanesulfonyl-chloride

5.5	trans-Quinoline-8-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	474	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	8-Quinoline-sulphonylchloride
5.6	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-C-phenyl-methanesulfonamide	437	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	alpha-Toluene-sulphonylchloride
5.7	trans-3,5-Dimethyl-isoxazole-4-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	442	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3,5 Dimethyl-isoxazol-sulphonylchloride
5.8	trans-Naphthalene-1-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	473	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	1-Naphthyl-sulphonylchloride
5.9	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-methoxy-N-methyl-benzenesulfonamide	453	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Methoxy-benzene-sulphonylchloride
5.10	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide	423	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Benzene-sulphonylchloride
5.11	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-fluoro-N-methyl-benzenesulfonamide	441	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Fluorobenzene-sulphonylchloride

5.12	trans-Thiophene-2-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	429	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2-Thiophene-sulphonylchloride
5.13	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2-fluoro-N-methyl-benzenesulfonamide	441	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2-Fluorobenzene-sulphonylchloride
5.14	trans-1-Methyl-1H-imidazole-4-sulfonic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	427	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	1-Methyl-imidazole-4-sulphonylchloride
5.15	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-tert-butyl-N-methyl-benzenesulfonamide	479	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-tert.-Butyl-benzene-sulphonylchloride
5.16	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-butoxy-N-methyl-benzenesulfonamide	495	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Butoxybenzene-sulphonylchloride
5.17	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-chloro-N-methyl-benzenesulfonamide	457 (1 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Chlorobenzene-sulphonylchloride
5.18	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	491	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Trifluoro-methylbenzene-sulphonylchloride

5.19	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-bromo-N-methyl-benzenesulfonamide	501 (1 Br)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Brombenzene-sulphonylchloride
5.20	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-nitro-benzenesulfonamide	468	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Nitrobenzene-sulphonylchloride
5.21	N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-chloro-N-methyl-benzenesulfonamide	457 (1 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3-chloro-phenyl sulfonylchloride
5.22	N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2,4-difluoro-N-methyl-benzenesulfonamide	459	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2,4-difluoro-phenyl-sulfonylchloride
5.23	N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2-bromo-N-methyl-benzenesulfonamide	501 (1 Br)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2-bromo-phenyl sulfonylchloride
5.24	N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-bromo-N-methyl-benzenesulfonamide	501 (1 Br)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3-bromo-phenyl sulfonylchloride
5.25	N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2,4-dichloro-N-methyl-benzenesulfonamide	491 (2 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2,4-dichloro-phenyl-sulfonylchloride

5.26	N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-fluoro-N-methyl-benzenesulfonamide	441	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3-fluoro-phenyl sulfonylchloride
5.27	N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3,4-dichloro-N-methyl-benzenesulfonamide	491 (2 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3,4-dichloro-phenyl-sulfonylchloride
5.28	N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2-chloro-N-methyl-benzenesulfonamide	457 (1 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2-chloro-phenyl sulfonylchloride
5.29	N-{4-trans-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3,4-difluoro-N-methyl-benzenesulfonamide	459	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3,4-difluoro-phenyl-sulfonylchloride
5.30	N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	463	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-trifluoromethyl-phenyl-sulfonylchloride
5.31	N-{4-trans-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-4-chloro-N-methyl-benzenesulfonamide	415 (1 Cl)	trans-(4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl)-methyl-amine	4-chloro-phenyl-sulfonylchloride
5.32	N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-4-chloro-N-methyl-benzenesulfonamide	429 (1 Cl)	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-chloro-phenyl-sulfonylchloride
5.33	N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-4-bromo-N-methyl-benzenesulfonamide	473 (1 Br)	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-bromo-phenyl-sulfonylchloride

5.34	N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-N-methyl-C-phenyl-methanesulfonamide	409	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	benzyl-sulfonylchloride
5.35	N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-4-fluoro-N-methyl-benzenesulfonamide	413	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-fluoro-phenyl-sulfonylchloride
5.36	N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-2-fluoro-N-methyl-benzenesulfonamide	413	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	2-fluoro-phenyl-sulfonylchloride
5.37	N-{4-trans-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-N-methyl-benzenesulfonamide	395	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	phenyl-sulfonylchloride
5.38	5-Chloro-thiophene-2-sulfonic acid {4-trans-[4-(allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-amide	436 (1 Cl)	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	5-Chloro-thiophene-2-sulfonylchloride

Example 6

A solution of 0.133 mmol amine in 0.5 ml dry DMF was treated subsequently with 0.17 mmol (1.3 equivalents) acid, 0.266 mmol (2 equvivalents) Huenig's base, 0.266 mmol (2 equivalents) N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride) (EDCI) as well as catalytic amount of Hydroxybenzotriazole (HOBT) (approximately 0.02 mmol). The solution was allowed to stand over night at room temperature. The resulting reaction mixture was treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation, the amide was obtained as a mixture of amino hydrochloride and formate. The following compounds were prepared from the corresponding amines and acids:

Example	Compound	MS MH^+	Amine	Acid
6.1	trans-Pyridine-2-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	388	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Picolinic acid
6.2	trans-1H-Indole-2-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	426	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	1H-Indole-2-carboxylic acid
6.3	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzamide	387	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Benzoic acid
6.4	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-chloro-N-methyl-benzamide	421 (1 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Chloro-benzoic acid

6.5	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-fluoro-N-methyl-benzamide	405	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Fluoro-benzoic acid
6.6	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-bromo-N-methyl-benzamide	465 (1 Br)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Bromo-benzoic acid
6.7	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzamide	455	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Trifluoro-methyl-benzoic acid
6.8	trans-Thiophene-3-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	393	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Thiophene-3-carboxylic acid
6.9	trans-5-Bromo-thiophene-2-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	471 (1 Br)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	5-Bromo-thiophene-2 carboxylic acid
6.10	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-2-thiophen-3-yl-acetamide	407	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2-Thiophene-3-yl-carboxylic acid
6.11	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2-(2,4-difluoro-phenyl)-N-methyl-acetamide	437	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2,4-Difluoro-acetic acid

6.12	trans-5-Fluoro-1H-indole-2-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	444	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	1H-Indole-5-Fluoro-2-carboxylic acid
6.13	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-2-(4-fluoro-phenyl)-N-methyl-acetamide	419	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Fluoro-phenylacetic acid
6.14	trans-1H-Indole-5-carboxylic acid {4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-amide	426	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	1H-Indole-5-carboxylic acid
6.15	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-chloro-N-methyl-benzamide	421 (1 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3-Chlorob-enzoic acid
6.16	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-fluoro-3,N-dimethyl-benzamide	419	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Fluor-3-Methyl-benzoic acid
6.17	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-nitro-benzamide	432	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Nitro-benzoic acid
6.18	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4,N-dimethyl-benzamide	401	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	p-Toluic acid

6.19	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-cyano-N-methyl-benzamide	412	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3-Cyano-benzoic acid
6.20	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3,N-dimethyl-benzamide	401	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	m-Toluoic acid
6.21	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3,4-dimethoxy-N-methyl-benzamide	447	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3,4 Dimethoxy-benzoic acid
6.22	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-methoxy-N-methyl-benzamide	417	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Methoxy-benzoic acid
6.23	trans-N-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-4-fluoro-N-methyl-3-nitro-benzamide	450	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Fluoro-3-nitro-benzoic acid
6.24	trans-4-Acetyl-N-{4-[6-(allyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzamide	429	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Acetyl-benzoic acid
6.25	trans-N-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzamide	469	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	4-Trifluoro-methyl-benzoic acid

6.26	trans-N-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzamide	441	trans-(4-[7-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Trifluoro-methyl-benzoic acid
6.27	trans-N-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-3-cyano-N-methyl-benzamide	384	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	3-Cyano-phenyl-benoic acid
6.28	trans-N-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-4-bromo-N-methyl-benzamide	451 (1 Br)	trans-(4-[7-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Bromo-phenyl-benzoic acid
6.29	trans-N-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-4-bromo-N-methyl-benzamide	337 (1 Br)	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-Bromo-phenyl-benzoic acid
6.30	trans-5-Bromo-thiophene-2-carboxylic acid {4-[4-(allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-amide	443 (1 Br)	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	2-Bromo-thiophene5-carboxylic acid
6.31	trans-N-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-4-fluoro-N-methyl-benzamide	391	trans-(4-[7-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Fluoro-phenyl-benzoic acid
6.32	trans-N-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-4-fluoro-N-methyl-benzamide	377	trans-(4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl)-methyl-amine	4-Fluoro-phenyl-benzoic acid

Example 7

A solution of 0.133 mmol amine was treated with 0.17 mmol (1.3 equivalents) isothiocyanate in 0.35 ml dry dioxane. The solution was allowed to stand over night at room temperature, treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation of the corresponding fraction, the thiourea was obtained as amino formate. The following compounds were prepared from the corresponding amines and isothiocyanates:

Example	Compound	MS MH^+	Amine	Isothiocyanate
7.1	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(2-bromo-4-fluoro-phenyl)-1-methyl-thiourea	514 (1 Br)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2-Bromo-4-fluoro-phenyl-isothiocyanate
7.2	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-bromo-2-methyl-phenyl)-1-methyl-thiourea	510 (1 Br)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Bromo-2-methyl-phenyl-isothiocyanate
7.3	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-(4-trifluoromethyl-phenyl)-thiourea	486	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Trifluoro-methyl-phenyl-isothiocyanate
7.4	trans1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-chloro-phenyl)-1-methyl-thiourea	452 (1 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Chloro-phenyl-isothiocyanate
7.5	trans1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-methoxy-phenyl)-1-methyl-thiourea	448	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Methoxy-phenyl-isothiocyanate

7.6	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-(4-cyano-phenyl)-1-methyl-thiourea	443	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Cyanophenyl-isothiocyanate
7.7	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-1-methyl-3-(3-methyl-butyl)-thiourea	412	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3-Methylbutyl-isothiocyanate
7.8	trans-1-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-3-sec-butyl-1-methyl-thiourea	398	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	sec-Butyl-isothiocyanate
7.9	trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-1-methyl-3-(4-trifluoromethyl-phenyl)-thiourea	458	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	1-Isothiocyanato-4-trifluoro-methyl-benzene
7.10	trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-3-(4-cyano-phenyl)-1-methyl-thiourea	415	trans-{4-[3-(Allyl-methyl-amino)-propoxy}-cyclohexyl}-methyl-amine	1-Isothiocyanato-4-cyano-benzene
7.11	trans-1-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-1-methyl-3-(3-methyl-butyl)-thiourea	384	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	1-Isothiocyanato-3-methyl-butane
7.12	trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-1-methyl-3-(4-trifluoromethyl-phenyl)-thiourea	500	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	1-Isothiocyanato-4-trifluoro-methyl-benzene

7.13	trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-3-(4-cyano-phenyl)-1-methyl-thiourea	457	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	1-Isothiocyanato-4-cyano-benzene
7.14	trans-1-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-1-methyl-3-(3-methyl-butyl)-thiourea	426	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	1-Isothiocyanato-3-methyl-butane
7.15	trans-1-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-1-methyl-3-(4-trifluoromethyl-phenyl)-thiourea	444	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	4-Trifluoro-methyl-phenyl-isothiocyanate

Example 8

The amine (3 eq.) was dissolved in CH_2Cl_2 (1 ml/mmol) and placed in an ice bath. A solution of chlorosulfonic acid (1 eq.) in CH_2Cl_2 (0.5 ml / mmol) was added slowly (30 min). The reaction mixture was stirred at 0 °C for a further 30 min. Afterward, the ice bath was removed and the stirring was continued for 1 h at room temperature. The precipitate was collected by filtration and dried under high vacuum. This salt was suspended in toluene (1 ml / mmol amine) and PCl_5 (1 eq) was added. The mixture was stirred at 75 °C for 2 h, cooled to room temperature and filtered. The solid residue was washed with toluene. The filtrate was evaporated and dried under high vacuum. The crude sulfamoyl chloride was used in the next step without further purification. The following sulfamoyl chlorides were prepared according to the above procedure from the corresponding amine:

Benzylsulfamoyl chloride, Phenylsulfamoyl chloride, 2,4-Difluoro-phenylsulfamoyl chloride, 2,5-Difluoro-phenylsulfamoyl chloride, 3,4-Difluoro-phenylsulfamoyl chloride, 3-Fluoro phenyl-sulfamoyl chloride, 4-Fluoro-phenylsulfamoyl chloride, 4-Chloro-phenylsulfamoyl chloride, 4-Bromo-phenylsulfamoyl chloride, 4-Methyl-phenylsulfamoyl chloride, 4-trifluoromethyl-phenylsulfamoyl chloride, 4-Cyano-phenylsulfamoyl chloride, 4-Methoxy-phenylsulfamoyl chloride, Butylsulfamoyl chloride, Phenethylsulfamoyl chloride, Cyclopropylsulfamoyl chloride, 2,2,2-Trifluoroethylsulfamoyl chloride, 4-Fluoro-benzylsulfamoyl chloride, Furan-2-ylmethylsulfamoyl chloride, Benzo[1,3]dioxol-5-ylmethylsulfamoyl chloride.

Example 9

The amine·hydrochloride (1 eq.) was dissolved in CH_3CN and placed in an ice bath. Sulfuryl chloride (3 eq.) was added slowly (20 min). The reaction mixture was stirred at room temperature for 15 min and at 65 °C for 20 h. The solvent was evaporated and the residue was dried under high vacuum. The crude sulfamoyl chloride was used in the next step without further purification. The following sulfamoyl chlorides were prepared according to the above procedure from the corresponding amine:

Chlorosulfonylamino-acetic acid ethyl ester, 4-(Chlorosulfonylamino-methyl)-benzoic acid methyl ester

Example 10

A solution of 0.135 mmol amine in 0.75 ml dry dioxane was treated with 5 equivalente of triethylamine followed by a solution of 0.175 mmol (1.3 equivalente) sulfamoylchloride in 0.25 ml dry dioxane. The suspension was allowed to stand over night at room temperature, treated with 0.15 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation of the corresponding fraction, the sulfamide was obtained as a mixture of amino hydrochloride and formate. The following compounds were prepared from the corresponding amines and sulfamoylchlorides:

Example	Compound	MS MH^+	Amine	Sulfamoyl-chloride
10.1	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-sulfamic acid benzyl amide	452	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Benzyl-sulfamoylchloride
10.2	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid phenyl amide	438	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Phenyl-sulfamoylchloride
10.3	trans-4-[({4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamoyloxy)-methyl]-benzoic acid methyl ester	510	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-(Chloro-sulfonylamino-methyl)-benzoic acid methyl ester
10.4	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid butyl amide	418	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Butyl-sulfamoylchloride

10.5	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid phenethyl amide	466	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Phenethyl-sulfamoylchloride
10.6	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid furan-2-ylmethyl amide	442	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Furan-2-yl-methyl-sulfamoylchloride
10.7	trans-({4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfonylamino)-acetic acid ethyl ester	448	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Chloro-sulfonylamino-acetic acid ethyl ester
10.8	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid cyclopropyl amide	402	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Cyclopropyl-sulfamoylchloride
10.9	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid 2,2,2-trifluoro-ethyl amide	444	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2,2,2-Trifluoro-ethyl-sulfamoylchloride
10.10	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid benzo[1,3]dioxol-5-ylmethyl amide	496	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	Benzo[1,3]dioxol-5-yl-methyl-sulfamoylchloride
10.11	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid 4-fluorobenzyl amide	470	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Fluoro-benzyl-sulfamoylchloride

10.12	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-chloro-phenyl)-amide	472 (1 Cl)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Chloro-phenyl-sulfamoylchloride
10.13	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-fluoro-phenyl)-amide	456	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Fluoro-phenyl-sulfamoylchloride
10.14	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-bromo-phenyl)-amide	516 (1 Br)	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Bromo-phenyl-sulfamoylchloride
10.15	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (p-tolyl)-amide	452	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	p-tolyl-sulfamoylchloride
10.16	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (3,4-difluoro-phenyl)-amide	474	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3,4-Difluoro-phenyl-sulfamoylchloride
10.17	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-trifluoromethyl-phenyl)-amide	506	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Trifluoro-methylphenyl-sulfamoylchloride
10.18	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (3-fluoro-phenyl)-amide	456	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	3-Fluoro-phenyl-sulfamoylchloride

10.19	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-cyano-phenyl)-amide	463	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Cyano-phenyl-sulfamoylchloride
10.20	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (2,4-difluoro-phenyl)-amide	474	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2,4-Difluoro-phenyl-sulfamoylchloride
10.21	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (4-methoxy-phenyl)-amide	468	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	4-Methoxy-phenyl-sulfamoylchloride
10.22	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-sulfamic acid (2,5-difluoro-phenyl)-amide	474	trans-[4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl]-methyl-amine	2,5-Difluoro-phenyl-sulfamoylchloride
10.23	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid benzyl amide	436 $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	Benzyl-sulfamoylchloride
10.24	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid phenyl amide	422 $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	Phenyl-sulfamoylchloride
10.25	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-chlorophenyl amide	456 (1 Cl) $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Chloro-phenyl-sulfamoylchloride

10.26	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-bromophenyl amide	500 (1 Br) $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Bromo-phenyl-sulfamoylchloride
10.27	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-methylphenyl amide	436 $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Methyl-phenyl-sulfamoylchloride
10.28	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-trifluoromethylphenyl amide	490 $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Trifluoro-methyl-phenyl-sulfamoylchloride
10.29	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-cyanophenyl amide	447 $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Cyano-phenyl-sulfamoylchloride
10.30	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid p-methoxyphenyl amide	452 $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	4-Methoxy-phenyl-sulfamoylchloride
10.31	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid 3,4-difluorophenyl amide	458 $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	3,4-Difluoro-phenyl-sulfamoylchloride
10.32	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid 3-fluorophenyl amide	440 $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	3-Fluoro-phenyl-sulfamoylchloride

10.33	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid 2,4-difluorophenyl amide	458 $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	2,4-Difluoro-phenyl-sulfamoylchloride
10.34	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-sulfamic acid 2,5-difluorophenyl amide	458 $M-H^-$	trans-(4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl)-methyl-amine	2,5-Difluoro-phenyl-sulfamoylchloride
10.35	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-sulfamic acid phenyl amide	396	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	Phenyl-sulfamoylchloride
10.36	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-sulfamic acid 3,4-difluorophenyl amide	432	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	3,4-Difluoro-phenyl-sulfamoylchloride
10.37	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-sulfamic acid 4-chlorophenyl amide	430 (1 Cl)	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	4-Chloro-phenyl-sulfamoylchloride
10.38	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-sulfamic acid benzyl amide	410	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	Benzyl-sulfamoylchloride
10.39	trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamic acid phenyl amide	410	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	Phenyl-sulfamoylchloride
10.40	trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamic acid 3-fluoro phenyl amide	428	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	3-Fluoro-phenyl-sulfamoylchloride

10.41	trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamic acid 3,4-difluoro phenyl amide	446	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	3,4-Difluoro-phenyl-sulfamoylchloride
10.42	trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamic acid 4-chloro phenyl amide	444 (1 Cl)	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	4-Chloro-phenyl-sulfamoylchloride
10.43	trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamic acid benzyl amide	424	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	Benzyl-sulfamoylchloride
10.44	trans-({4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-sulfamoylamino)-acetic acid ethyl ester	420	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-amine	Chloro-sulfonylamino-acetic acid ethyl ester
10.45	trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid phenyl amide	452	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	Phenyl-sulfamoylchloride
10.46	trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid 3-fluoro-phenyl amide	470	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	3-Fluoro-phenyl-sulfamoylchloride
10.47	trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid 3,4-difluoro-phenyl amide	488	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	3,4-Difluoro-phenyl-sulfamoylchloride
10.48	trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid 4-chloro-phenyl amide	486 (1 Cl)	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	4-Chloro-phenyl-sulfamoylchloride

10.49	trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid furan-2-ylmethyl amide	456	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	Furan-2-yl-methyl-sulfamoylchloride
10.50	trans-{4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamic acid benzyl amide	466	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	Benzylsulfamoylchloride
10.51	trans-({4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl}-methyl-sulfamoyloxy)-acetic acid ethyl amide	462	trans-(4-[7-(Allyl-methyl-amino)-heptyloxy]-cyclohexyl)-methyl-amine	Chlorosulfonyl-amino-acetic acid ethyl ester

Example 11

11.1

4.01 g (31 mmol) of trans-4-methylamino-cyclohexanol (twice suspended in toluene and evaporated under reduced pressure to remove water) were suspended in 60 ml hexamethyldisilazane and refluxed for 2.5 h. The solution was evaporated under reduced pressure, dissolved in 80 ml CH_2Cl_2 and added to a cooled solution (0 °C) of 2.06 ml (17.05 mmol) trichloromethylchloroformate (diphosgene) and 4.40 ml (34.10 mmol) quinoline. The reaction was stirred for 3 h at 0 °C and evaporated. The residue and 8.47 g (65.1 mmol) 3,4-difluorophenol were dissolved in 220 ml THF, treated at 0 °C in small portions with 3.25 g (74.4 mmol) of NaH (ca 55% in oil) and 0.26 g (1.6 mmol) of KI. The reaction was stirred at room temperature over night, cooled (0 °C) and after the addition of 0.68 g (15.5 mmol) of NaH (ca 55% in oil) stirred at RT for 24 h. After the addition of 60 ml water, the pH was adjusted to pH 2 (1 N HCl) and the reaction mixture was stirred for 1 h. The reaction was partitioned between aqueous 1 N NaOH/Et_2O (3x300 ml), the organic phases were dried over Na_2SO_4 and evaporated. The residue was dissolved in 200 ml THF/dioxane (1:1). 34 ml 1 N NaOH were added at 0 °C and the mixture was stirred for 3 h. The reaction was partitioned between water/Et_2O (3x300), the organic phase was dried over Na_2SO_4 and evaporated to yield 11.6 g crude trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid 3,4-difluoro-phenyl ester.

11.2

A solution of 11.6 g (containing 31 mmol) of crude trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid 3,4-difluoro-phenyl ester in 110 ml of 1,4-dibromobutane was treated with 3.16 g (9.3 mmol) tetrabutylammonium hydrogen sulfate and 200 ml of aqueous 50% NaOH and stirred for 2.5 days at RT. The reaction was extracted (CH_2Cl_2 2x). The organic phase was dried over Na_2SO_4, evaporated and purified by flash silica gel column (first with hexane to remove the dibromobutane and then hexane/ EtOAc 1:1) to yield 4.06 g (31 %) of trans-[4-(4-bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester, MS: 420 (M, 1Br).

11.3

In analogy to example 11.1 and 11.2, reaction of trans-4-Methylamino-cyclohexanol with alpha, alpha, alpha-trifluoro-p-cresol followed by reaction with 1,4-dibromobutane yielded trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester, MS: 452 (MH^+, 1Br).

11.4

To a solution of 16.1 g (124.7 mmol) trans-4-methylamino-cyclohexanol in 40 ml CH_2Cl_2, 18.3 ml (130.9 mmol, 1.05 eq) 4-chlorophenylchloroformate and 22.4ml (130.9 mmol, 1.05 eq) Huenigs base were added at 0°C. The solution was stirred at RT over night, diluted, and washed with 1M HCl, sat. aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$. Column chromatography on silica gel with EtOAc:hexane 1:1 yielded 32.2 g (91%) trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester as white solid , MS: 283 (M, 1Cl).

11.5

To 1.46 g (5.1 mmol) trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester suspended in 30 ml (190.4 mmol, 37 eq) 1,6-Dibomhexane, 0.53g (1.5 mmol, 0.3 eq) tetrabutylammoniumhydrogensulfate and 30 ml 50% aqueous NaOH were added. The mixture was stirred at 50°C for 1 day, CH_2Cl_2 was added and the layers were separated. The inorganic layer was extracted with CH_2Cl_2, the combined organic layers were washed with brine and dried over $MgSO_4$. The excess of dibromide was removed in vacuo and the residue purified by column chromatography on silica gel with hexane:EtOAc 4:1 as eluent yielding 2.04 g (89%) trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester as light yellow oil , MS: 446 (M, 1Br, 1Cl).

11.6

In analogy to example 11.5, trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester and 1,4-dibrombutane were reacted to yield trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester as yellowish oil, MS: 418 (M, 1Br, 1Cl);

11.7

In analogy to example 11.5, trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester and 1,5-dibromopentane were reacted to yield trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester as yellow oil, MS: 433 (MH^+, 1Br, 1Cl);

11.8

At 0°C, to a solution of 1.26 ml (14.1 mmol) 3-bromo-1-propanol and 3.5 ml (15.3 mmol) 2,6-di-tert-butylpyridine in 7 ml CH_2Cl_2, a solution of 2.49 ml (14.8 mmol) trifluoromethansulfonic anhydride in 3.6 ml CH_2Cl_2 was added. After 2.5 h stirring at 0°C, the solution was evaporated, dissolved in 7 ml nitromethane and treated with a solution of 2.0 g (7 mmol) trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester

and 3.23 ml (14.1 mmol) 2,6-di-tert-butylpyridine in 27 ml nitromethane. The reaction mixture was heated to 60 °C for 3.5 h and then diluted with EtOAc, washed with 1M HCl, sat. aqueous $NaHCO_3$, and water, dried over $MgSO_4$ and evaporated. Purification by flash-chromatography on silica gel with hexane/EtOAc 9:1 yielded trans-[4-(3-Bromo-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester as yellow oil, MS: 405 (MH^+, 1Br, 1Cl).

11.9

To 3 g (23.2 mmol) trans-4-Methylamino-cyclohexanol in 120 ml CH_2Cl_2 were added 4.2 ml (24.4 mmol, 1.05 eq) N,N-diisopropylethylamine followed by 5.96 g (24.4 mmol, 1.05 eq) 4-(trifluoromethyl)-benzenesulfonyl in 50 ml CH_2Cl_2. The mixture was stirred at RT over night and the organic phase extracted with 1M $KHSO_4$, followed by 5% $NaHCO_3$ and brine. The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Column chromatography on silica gel with hexane:EtOAc 1:1 yielded 6.0 g (77%) trans-N-(4-Hydroxy-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide as off-white solid, MS: 338 (MH^+).

11.10

In analogy to example 11.9. trans-4-Methylamino-cyclohexanol and 4-bromobenzenesulfonylchloride were reacted to yield trans-4-Bromo-N-(4-hydroxy-cyclohexyl)-N-methyl-benzenesulfonamide as off-white solid, MS: 348 (MH^+, 1Br).

11.11

6 g (17.8 mmol) trans-N-(4-Hydroxy-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide were suspended in 100 ml (658 mmol, 37 eq) 1,6-dibromohexane and 1.8 g (5.3 mmol, 0.3 eq) tetra-butylammonium hydrogensulfate and 100 ml 50% aqueous NaOH were added. The reaction mixture was stirred at 50°C for 2 days, CH_2Cl_2 was added and the layers were separated. The inorganic phase was extracted with CH_2Cl_2, the combined inorganic phases were washed with brine and dried over Na_2SO_4 and evaporated. The excess of the dibromide was removed in vacuo and the residue purified by column chromatography on silica gel with hexane: EtOAc 4:1 yielding 8.3 g (93%) trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide as yellow oil, MS: 500 (MH^+, 1Br).

11.12

In analogy to example 11.11, trans-4-Bromo-N-(4-hydroxy-cyclohexyl)-N-methyl-benzenesulfonamide and 1,6-dibromohexane were reacted to yield trans-4-Bromo-N-[4-

(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide as off-white solid, MS: 510 (MH^+, 1Br).

Example 12

A solution of 0.25 mmol (1 equivalent) bromide in 0.7 ml dry DMA was treated with a solution of 0.5 mmol (2 equivalents) secondary amine in 0.15 ml dry DMA at room temperature. After 16 h, 2 equivalents of secondary amine were added again to the solution. The reaction mixture was allowed to stand over night at room temperature, treated with 0.2 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation, the tertiary amine was obtained as a mixture of amino hydrobromide and formate. The following compounds were prepared from the corresponding bromides and secondary amines:

Example	Compound	MS MH^+	Bromide	Secondary amine
12.1	trans-(4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	461	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	2-Ethylamino-ethanol
12.2	trans-[4-(4-Diethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	445	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	Diethylamine
12.3	trans-[4-(4-Dimethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	417	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	Dimethylamin
12.4	trans-(4-{4-[Bis-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	477	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	Diethanolamine

12.5	trans-Methyl-{4-[4-(methyl-propyl-amino)-butoxy]-cyclohexyl}-carbamic acid 4-trifluoromethyl-phenyl ester	445	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester	N-Methylpropyl-amine
12.6	{4-[Trans-4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 3,4-difluoro-phenyl ester	411	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester;	Allylmethylamine
12.7	[trans-4-(4-Dimethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	385	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	Dimethylamine
12.8	(trans-4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 3,4-difluoro-phenyl ester	429	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	Ethyl-(2-hydroxy-ethyl)-amine
12.9	[trans-4-(4-Diethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	413	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	Diethylamine
12.10	Methyl-[trans-4-(4-piperidin-1-yl-butoxy)-cyclohexyl]-carbamic acid 3,4-difluoro-phenyl ester	425	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	Piperidine
12.11	[trans-4-(4-Azetidin-1-yl-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	397	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	Azetidine

12.12	Methyl-[trans-4-(4-morpholin-4-yl-butoxy)-cyclohexyl]-carbamic acid 3,4-difluoro-phenyl ester	427	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	Morpholine
12.13	Methyl-[trans-4-(4-pyrrolidin-1-yl-butoxy)-cyclohexyl]-carbamic acid 3,4-difluoro-phenyl ester	411	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	Pyrrolidine
12.14	(4-{trans-4-[Ethyl-(2-methoxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 3,4-difluoro-phenyl ester	443	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	Ethyl-(2-methoxy-ethyl)-amine
12.15	trans-Methyl-{4-[4-(methyl-propyl-amino)-butoxy]-cyclohexyl}-carbamic acid 3,4-difluoro-phenyl ester	413	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 3,4-difluoro-phenyl ester	N-Methylpropyl-amine

The following compounds were further prepared from the corresponding bromides and secondary amines:

Example	Compound	MS MH^+	Bromide	Secondary amine
12.16	trans-N-(4-{3-[Ethyl-(2-methoxy-ethyl)-amino]-propoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	481	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-(2-methoxy-ethyl)-ethylamine
12.17	trans-N-{4-[3-(3,6-Dihydro-2H-pyridin-1-yl)-propoxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	461	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	1,2,3,6-Tetra-hydro-pyridine

12.18	trans-N-Methyl-N-{4-[3-(methyl-propyl-amino)-propoxy]- cyclohexyl}-4-trifluoromethyl-benzenesulfonamide	451	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Methylpropyl-amine
12.19	trans-N-(4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	481	trans-N-[4-(4-Bromo-butoxy)- cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	2-(Ethylamino)-ethanol
12.20	trans-N-[4-(4-Diethylamino-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	465	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Diethylamine
12.21	trans-N-[4-(4-Dimethylamino-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	437	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Dimethylamine
12.22	trans-N-(4-{4-[(2-Methoxy-ethyl)-methyl-amino]-butoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	481	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-(2-Methoxy-ethyl)-methyl-amine
12.23	trans-N-(4-{4-[(2-Hydroxy-ethyl)-methyl-amino]-butoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	467	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	2-(Methylamino)-ethanol
12.24	trans-N-(4-{4-[Bis-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	497	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Diethanolamine

12.25	trans-N-{4-[4-(Cyclopropylmethyl-methyl-amino)-butoxy]- cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	477	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Cyclopropyl-methyl-methyl-amine
12.26	trans-N-Methyl-N-[4-(4-morpholin-4-yl-butoxy)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide	479	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Morpholine
12.27	trans-N-{4-[4-(3,6-Dihydro-2H-pyridin-1-yl)-butoxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	475	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	1,2,3,6-Tetra-hydro-pyridine
12.28	trans-N-Methyl-N-{4-[4-(methyl-propyl-amino)-butoxy]- cyclohexyl}-4-trifluoromethyl-benzenesulfonamide	465	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Methylpropyl-amine
12.29	trans-N-(4-{4-[Ethyl-(2-methoxy-ethyl)-amino]-butoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	495	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-(2-methoxy-ethyl)-ethylamine
12.30	trans-N-(4-{3-[(2-Methoxy-ethyl)-methyl-amino]-propoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	467	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-(2-Methoxy-ethyl)-methyl-amine
12.31	trans-N-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}N-methyl4-trifluoromethyl-benzenesulfonamide	449	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Methylallyl-amine

12.32	trans-N-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxy}-cyclohexyl) N-methyl-4-trifluoromethyl-benzenesulfonamide	467	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	2-(Ethylamino)-ethanol
12.33	trans-N-[4-(3-Diethylamino-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	451	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Diethylamine
12.34	trans-N-(4-{3-[(2-Hydroxy-ethyl)-methyl-amino]-propoxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	453	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	2-(Methylamino)-ethanol
12.35	trans-N-(4-{3-[Bis-(2-hydroxy-ethyl)-amino]-propoxy}-cyclohexyl) N-methyl-4-trifluoromethyl-benzenesulfonamide	483	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Diethanol-amine
12.36	trans-N-{4-[3-(Cyclopropylmethyl-methyl-amino)-propoxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	463	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Cyclopropyl-methyl-methyl-amine
12.37	trans-N-Methyl-N-[4-(3-pyrrolidin-1-yl-propoxy)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide	449	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Pyrrolidine
12.38	trans-N-Methyl-N-[4-(3-morpholin-4-yl-propoxy)-cyclohexyl]- 4-trifluoromethyl-benzenesulfonamide	465	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Morpholine

Example 13

1 eq of the bromide is treated with 3 eq of amine in (4-10 ml/mmol bromide) DMA at RT until no starting material can be detected with TLC. The solution is concentrated and the residue is redissolved in CH_2Cl_2/ 5% aqueous $NaHCO_3$. The phases are separated, and the inorganic phase is extracted with CH_2Cl_2, the combined organic phases are washed with brine, dried over Na_2SO_4.The crude material is purified by flash chromatography. The following compounds were prepared from the corresponding bromides and amines:

Example	Compound	MS MH^+	Bromide	Amine
13.1	trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester	409 (1 Cl)	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Allylmethylamine
13.2	trans-{4-[5-(Allyl-methyl-amino)-pentyloxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester	424 (1 Cl)	trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Allylmethylamine
13.3	trans-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	411 (1 Cl)	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Dimethylamine
13.4	trans-[4-(4-Dimethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	383 (1 Cl)	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Dimethylamine
13.5	trans-[4-(5-Dimethylamino-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	397 (1 Cl)	trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Dimethylamine

13.6	trans-(4-{6-[Ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	456 (1 Cl)	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	2-Ethylamino-ethanol
13.7	trans-(4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	427 (1 Cl)	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	2-Ethylamino-ethanol
13.8	trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	442 (1 Cl)	trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	2-Ethylamino-ethanol
13.9	trans-(4-{6-[Ethyl-(2-methoxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	470 (1 Cl)	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	N-(2-Methoxyethyl)-ethylamine
13.10	trans-(4-{4-[Ethyl-(2-methoxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	442 (1 Cl)	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	N-(2-Methoxyethyl)-ethylamine
13.11	trans-{4-[3-(Allyl-methyl-amino)-propoxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester	395 (1 Cl)	trans-[4-(3-Bromo-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Allylmethylamine
13.12	trans-(4-{3-[Ethyl-(2-methoxy-ethyl)-amino]-propoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	427 (1 Cl)	trans-[4-(3-Bromo-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	N-(2-Methoxyethyl)-ethylamine

13.13	trans-(4-{5-[Ethyl-(2-methoxy-ethyl)-amino]-pentyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	456 (1 Cl)	trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	N-(2-Methoxyethyl)-ethylamine
13.14	trans-[4-(3-Dimethylamino-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	369 (1 Cl)	trans-[4-(3-Bromo-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Dimethylamine
13.15	trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	413 (1 Cl)	trans-[4-(3-Bromo-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	2-Ethylamino-ethanol
13.16	trans-Methyl-[4-(3-piperidin-1-yl-propoxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester	409 (1 Cl)	trans-[4-(3-Bromo-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Piperidine
13.17	trans-Methyl-[4-(4-piperidin-1-yl-butoxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester	424 (1 Cl)	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Piperidine
13.18	trans-Methyl-[4-(6-piperidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester	452 (1 Cl)	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Piperidine
13.19	trans-Methyl-[4-(5-piperidin-1-yl-pentyloxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester	438 (1 Cl)	trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Piperidine
13.20	trans-[4-(3-Diethylamino-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	397 (1 Cl)	trans-[4-(3-Bromo-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Diethylamine

13.21	trans-[4-(6-Diethylamino-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	440 (1 Cl)	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Diethylamine
13.22	trans-[4-(4-Diethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	411 (1 Cl)	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Diethylamine
13.23	trans-[4-(5-Diethylamino-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	426 (1 Cl)	trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Diethylamine
13.24	trans-Methyl-[4-(3-pyrrolidin-1-yl-propoxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester	395 (1 Cl)	trans-[4-(3-Bromo-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Pyrrolidine
13.25	trans-Methyl-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester	436 (1 Cl) $M-H^-$	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Pyrrolidine
13.26	trans-(4-{6-[(2-Hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	442 (1 Cl)	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	2-(Methylamino)-ethanol
13.27	trans-(4-{4-[(2-Hydroxy-ethyl)-methyl-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	413 (1 Cl)	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	2-(Methylamino)-ethanol

13.28	trans-(4-{5-[(2-Hydroxy-ethyl)-methyl-amino]-pentyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	427 (1 Cl)	trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	2-(Methylamino)-ethanol
13.29	trans-Methyl-[4-(4-pyrrolidin-1-yl-butoxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester	409 (1 Cl)	trans-[4-(4-Bromo-butoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Pyrrolidine
13.30	trans-Methyl-[4-(5-pyrrolidin-1-yl-pentyloxy)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester	424 (1 Cl)	trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	Pyrrolidine
13.31	trans-(4-{3-[(2-Hydroxy-ethyl)-methyl-amino]-propoxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	399 (1 Cl)	trans-[4-(3-Bromo-propoxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester	2-(Methylamino)-ethanol

The following compounds were further prepared from the corresponding bromides and amines:

Example	Compound	MS MH^+	Educt 1	Educt 2
13.32	trans-N-(4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl)-4-bromo-N-methyl-benzenesulfonamide	501 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	N-Allylmethyl-amine
13.33	trans-4-Bromo-N-[4-(6-dimethylamino-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	475 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Dimethylamine

13.34	trans-4-Bromo-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-benzenesulfonamide	519 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	N-(2-Methoxy-ethyl)methyl-amine
13.35	trans-N-(4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	528	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Allylmethyl-amine
13.36	trans-N-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	465	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Dimethylamine
13.37	trans-N-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	509	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-(2-Methoxy-ethyl)methyl-amine
13.38	trans-4-Bromo-N-[4-(6-diethylamino-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	503 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Diethylamine
13.39	trans-4-Bromo-N-{4-[6-(isopropyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide	503 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Isopropylmethyl-amine
13.40	trans-4-Bromo-N-methyl-N-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-benzenesulfonamide	501 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Pyrrolidine

13.41	trans-N-[4-(6-Diethylamino-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	493	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Diethylamine
13.42	trans-N-{4-[6-(Isopropyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	493	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Isopropylmethyl-amine
13.43	trans-N-Methyl-N-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide	491	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Pyrrolidine

Example 14

A solution of the secondary amine (0.6 mmol; 3.5 equivalents) in 0.7 ml dry DMF is treated with 0.17 mmol (1 equivalent) of the bromide in 0.25 ml dry DMF, as well as with 0.17 mmol (1 equivalent) 1,8-Diazabicyclo[5.4.0]undec-7-ene(1,5-5) (DBU). The reaction mixture is shaken over night at 50°C, then treated with 0.2 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation, the tertiary amine is obtained as a mixture of amino formate and hydrobromide. The following compounds can be prepared from the corresponding bromides and secondary amines:

Example	Compound	MS MH^+	Bromide	Secondary amine
14.1	trans-4-Bromo-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-benzenesulfonamide	519 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	N-(2-methoxy-ethyl)methyl-amine
14.2	trans-N-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	509	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-(2-methoxy-ethyl)methyl-amine
14.3	trans-4-Bromo-N-methyl-N-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-benzenesulfonamide	517 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Morpholine
14.4	trans-N-[4-(6-Azetidin-1-yl-hexyloxy)-cyclohexyl]-4-bromo-N-methyl-benzenesulfonamide	487 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Trimethylene-amine
14.5	trans-4-Bromo-N-{4-[6-(butyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide	517 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	N-Methylbutyl-amine

14.6	trans-4-Bromo-N-methyl-N-[4-(6-piperidin-1-yl-hexyloxy)-cyclohexyl]-benzenesulfonamide	515 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Piperidine
14.7	trans-4-Bromo-N-{4-[6-(3,6-dihydro-2H-pyridin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide	513 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	1,2,3,6-Tetra-hydro-pyridine
14.8	trans-4-Bromo-N-(4-{6-[ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-N-methyl-benzenesulfonamide	519 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	2-(Ethylamino)-ethanol
14.9	trans-4-Bromo-N-{4-[6-(3-hydroxy-pyrrolidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide	517 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	(R)-3-Hydroxy-pyrrolidine
14.10	trans-4-Bromo-N-methyl-N-{4-[6-(methyl-propyl-amino)-hexyloxy]-cyclohexyl}-benzenesulfonamide	503 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	N-Methyl-N-propylamine
14.11	trans-4-Bromo-N-[4-(6-diallylamino-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	527 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Diallylamine
14.12	trans-4-Bromo-N-{4-[6-(4-hydroxymethyl-piperidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide	545 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	4-Hydroxy-methyl-piperidine
14.13	trans-4-Bromo-N-(4-{6-[(2-hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-benzenesulfonamide	505 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	2-Hydroxyethyl-methylamine

14.14	trans-4-Bromo-N-methyl-N-{4-[6-(4-methyl-piperidin-1-yl)-hexyloxy]-cyclohexyl}-benzenesulfonamide	529 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	4-Methyl-piperidine
14.15	trans-4-Bromo-N-{4-[6-(4-hydroxy-piperidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide	531 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	4-Hydroxy-piperidine
14.16	trans-4-Bromo-N-{4-[6-(cyclopropylmethyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide	515 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	N-Methyl-cyclopropane-methylamine
14.17	trans-[(6-{4-[(4-Bromo-benzenesulfonyl)-methyl-amino]-cyclohexyloxy}-hexyl)-methyl-amino]-acetic acid ethyl ester	547 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Sarcosine ethyl ester hydro-chloride
14.18	trans-N-Methyl-N-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide	507	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Morpholine
14.19	trans-N-[4-(6-Azetidin-1-yl-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	477	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Trimethylene-amine
14.20	trans-N-{4-[6-(Butyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	507	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Methylbutyl-amine

14.21	trans-N-Methyl-N-[4-(6-piperidin-1-yl-hexyloxy)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide	505	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Piperidine
14.22	trans-N-{4-[6-(3,6-Dihydro-2H-pyridin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	503	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	1,2,3,6-Tetra-hydro-pyridine
14.23	trans-N-(4-{6-[Ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	509	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	2-(Ethylamino)-ethanol
14.24	trans-N-{4-[6-(3-Hydroxy-pyrrolidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	507	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	(R)-3-Hydroxy-pyrrolidine
14.25	trans-N-Methyl-N-{4-[6-(methyl-propyl-amino)-hexyloxy]-cyclohexyl}-4-trifluoromethyl-benzenesulfonamide	493	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Methyl-N-propylamine
14.26	trans-N-[4-(6-Diallylamino-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	517	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Diallylamine
14.27	trans-N-{4-[6-(4-Hydroxymethyl-piperidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	535	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	4-Hydroxy-methylpiperidine

14.28	trans-N-(4-{6-[(2-Hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide	495	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	2-Hydroxyethyl-methylamine
14.29	trans-N-{4-[6-(4-Hydroxy-piperidin-1-yl)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	521	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	4-Hydroxy-piperidine
14.30	trans-N-{4-[6-(Cyclopropylmethyl-methyl-amino)-hexyloxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	505	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Methyl-cyclopropane-methylamine
14.31	trans-[Methyl-(6-{4-[methyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-cyclohexyloxy}-hexyl)-amino]-acetic acid ethyl ester	537	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Sarcosine ethyl ester hydro-chloride

Example 15

A solution of 1.02 mmol (6 equivalents) primary amine in 0.7 ml dry DMF was treated with 0.17mmol (1 equivalent) bromide in 0.25 ml dry DMF, as well as with 0.17 mmol (1 equivalent), 1,8-Diazabicyclo[5.4.0]undec-7-ene(1,5-5) (DBU). The reaction mixture was shaken over night at 50°C, treated with 0.2 ml formic acid and purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation, the secondary amine was obtained as a mixture of amino formates and hydrobromides.The following compounds were prepared from the corresponding bromides and amines:

Example	Compound	MS MH^+	Bromide	Amine
15.1	trans-N-[4-(6-Allylamino-hexyloxy)-cyclohexyl]-4-bromo-N-methyl-benzenesulfonamide	487 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Allylamine
15.2	trans-4-Bromo-N-{4-[6-(2-hydroxy-ethylamino)-hexyloxy]-cyclohexyl}-N-methyl-benzenesulfonamide	491 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	2-Ethanolamine
15.3	trans-4-Bromo-N-[4-(6-ethylamino-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	475 (1 Br)	trans-4-Bromo-N-[4-(6-bromo-hexyloxy)-cyclohexyl]-N-methyl-benzenesulfonamide	Ethylamine
15.4	trans-N-{4-[4-(2-Hydroxy-ethylamino)-butoxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	453	trans-N-[4-(4-Bromo-butoxy)- cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Ethanolamine
15.5	trans-N-[4-(4-Ethylamino-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	437	trans-N-[4-(4-Bromo-butoxy)- cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Ethylamine

15.6	trans-N-{4-[3-(2-Hydroxy-ethylamino)-propoxy]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide	439	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Ethanolamine
15.7	trans-N-[4-(3-Ethylamino-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	423	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Ethylamine
15.8	trans-N-[4-(6-Allylamino-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	477	trans-N-[4-(6-Bromo-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Allylamine
15.9	trans-N-[4-(3-Allylamino-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	435	trans-N-[4-(3-Bromo-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	N-Methylallyl-amine
15.10	trans-N-[4-(4-Allylamino-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	449	trans-N-[4-(4-Bromo-butoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide	Allylamine

Example 16

16.1

To 10 g (40.1 mmol) trans-4-Hydroxy-cyclohexylcarbamic acid benzyl ester in 40 ml DMF, 4.09 g (60.1 mmol, 1.5 eq) imidazole and 6.65 g (44.1 mmol, 1.1 eq) TBDMSCl in 20 ml DMF were added at 0°C. The mixture was warmed to 50°C and stirred at that temperature for 2h. A saturated solution of $NaHCO_3$ was added, the mixture was concentrated and redissolved in ether/water. The phases were separated and the inorganic phase was extracted with ether. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified on silica gel with hexane:EtOAc 5:1 as eluent yielding 11.8 g (81%) trans-[4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexyl]-carbamic acid benzyl ester as colorless gum, MS: 348 ($M-CH_3$).

16.2

To a suspension of 0.58 g (55% in mineral oil, 13 mmol, 1.2eq) sodium hydride in 20 ml DMF, a solution of 4.2 g (11 mmol) trans-[4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexyl]-carbamic acid benzyl ester in 10 ml DMF was added slowly. The temperature was raised slowly to 50 °C and kept at that temperature for 1h. At RT 0.9 ml (14 mmol; 1.3 eq) iodomethane were added and the mixture stirred over night. Additional 0.58 g (55% in mineral oil, 13 mmol, 1.2eq) sodium hydride and 0.9 ml (14 mmol; 1.3 eq) iodomethane were added and the reaction mixture was stirred for 1 day. Aqueous NH_4Cl solution was added and the inorganic phase was extracted with ether, washed with brine, dried over Na_2SO_4 and evaporated yielding 3.1g (72%) trans-[4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexyl]-methyl-carbamic acid 2-ethylidene-hexa-3,5-dienyl ester.

16.3

To a solution of 3.1g (8 mmol) trans-[4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexyl]-methyl-carbamic acid 2-ethylidene-hexa-3,5-dienyl ester in 20ml THF, 10.3 ml (1M, 10.3 mmol, 1.3 eq) Tetrabutylammonium fluoride in THF were added at 6°C and the mixture was stirred at RT for 2 days. Water was added and the phases were separated and the inorganic phase was extracted with ether and EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4 and evaporated. Column chromatography on silica gel with a gradient EtOAc:hexane 1:4 – EtOAc yielded 1.9 g 1.9 g (92%) trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid benzyl ester as orange oil, MS: 263 (M).

16.4

In analogy to examples 16.2 and 16.3, from trans-[4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexyl]-carbamic acid benzyl ester and bromoethane, trans-Ethyl-(4-hydroxy-cyclohexyl)-carbamic acid benzyl ester was obtained as orange oil, MS: 277 (M).

16.5

In analogy to examples 16.2 and 16.3, from trans-[4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexyl]-carbamic acid benzyl ester and allyl bromide, trans-Allyl-(4-hydroxy-cyclohexyl)-carbamic acid benzyl ester was obtained as orange oil, MS: 289 (M).

16.6

In analogy to examples 16.2 and 16.3, from trans-[4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexyl]-carbamic acid benzyl ester and benzyl bromide, trans-Benzyl-(4-hydroxy-cyclohexyl)-carbamic acid benzyl ester was obtained as orange oil, MS: 340 (MH^+).

16.7

In analogy to examples 16.2 and 16.3, from trans-[4-(tert-Butyl-dimethyl-silanyloxy)-cyclohexyl]-carbamic acid benzyl ester and 2,4,5-trifluorobenzyl bromide, trans-(4-Hydroxy-cyclohexyl)-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester was obtained as orange oil, MS: 394 (MH^+).

16.8

To 1.9 g (7 mmol) trans-(4-Hydroxy-cyclohexyl)-methyl-carbamic acid benzyl ester suspended in 40.7 ml (267 mmol, 37 eq) 1,6-dibomohexane, 0.74 g (2.0 mmol, 0.3 eq) tetrabutyl ammonium hydrogensulfate and 40 ml 50% aqueous NaOH were added. The mixture was stirred at RT for 3 days, CH_2Cl_2 was added and the layers were separated. The inorganic layer was extracted with CH_2Cl_2, the combined organic layers were washed with brine and dried over Na_2SO_4. The excess of dibromide was removed in vacuo and the residue was purified by column chromatography on silica gel with hexane:EtOAc 4:1 as eluent yielding 2.0 g (64%) trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester as light yellow oil, MS: 425 (M, 1Br).

16.9

In analogy to example 16.8, trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester was obtained as light yellow liquid, MS: 439 (M, 1Br), from trans-Ethyl-(4-hydroxy-cyclohexyl)-carbamic acid benzyl ester.

16.10

In analogy to example 16.8, trans-Allyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester was obtained as light yellow liquid, MS: 451 (M, 1Br), from trans-Allyl-(4-hydroxy-cyclohexyl)-carbamic acid benzyl ester.

16.11

In analogy to example 16.8, trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic

acid benzyl ester was obtained as light yellow liquid, MS: 501 (M, 1Br), from trans-Benzyl-(4-hydroxy-cyclohexyl)-carbamic acid benzyl ester.

16.12

In analogy to example 16.8, trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester was obtained as light yellow liquid, MS: 555 (M, 1Br), from trans-(4-Hydroxy-cyclohexyl)-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester.

Example 17

1 eq of the bromide is treated with 3 eq of each amine in (1 ml/mmol bromide) DMF in the presence of 1 eq diisopropylethylamine and a catalytic amount of NaI at RT until no starting material can be detected with HPLC. Formic acid is added and the crude materials are purified by preparative HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After evaporation the amines were obtained as a mixture of amino formates and hydrobromides. The following compounds were prepared from the corresponding bromides and amines:

Example	Compound	MS MH^+	Bromide	Amine
17.1	trans-Ethyl-(4-{6-[ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester	449	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester	2-(Ethylamino)-ethanol
17.2	trans-Benzyl-(4-{6-[ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester	511	trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	2-(Ethylamino)-ethanol
17.3	trans-(4-{6-[Ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid benzyl ester	435	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester	2-(Ethylamino)-ethanol
17.4	trans-Allyl-(4-{6-[ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester	461	trans-Allyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	2-(Ethylamino)-ethanol
17.5	trans-(4-{6-[Ethyl-(2-hydroxy-ethyl)-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	565	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	2-(Ethylamino)-ethanol

17.6	trans-[4-(6-Azetidin-1-yl-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester	417	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester	Azetidine
17.7	trans-[4-(6-Azetidin-1-yl-hexyloxy)-cyclohexyl]-benzyl-carbamic acid benzyl ester	479	trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	Azetidine
17.8	trans-[4-(6-Azetidin-1-yl-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester	403	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester	Azetidine
17.9	trans-Ethyl-(4-{6-[(2-hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester	435	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester	2-(Methylamino)-ethanol
17.10	trans-Benzyl-(4-{6-[(2-hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester	497	trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	2-(Methylamino)-ethanol
17.11	trans-(4-{6-[(2-Hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid benzyl ester	421	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester	2-(Methylamino)-ethanol
17.12	trans-Allyl-(4-{6-[(2-hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester	447	trans-Allyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	2-(Methylamino)-ethanol

17.13	trans-(4-{6-[(2-Hydroxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	551	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	2-(Methylamino)-ethanol
17.14	trans-Ethyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester	449	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester	N-(2-Methoxy-ethyl)-methyl-amine
17.15	trans-Benzyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid benzyl ester	511	trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	N-(2-Methoxy-ethyl)-methyl-amine
17.16	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid benzyl ester	435	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester	N-(2-Methoxy-ethyl)-methyl-amine
17.17	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	565	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	N-(2-Methoxy-ethyl)-methyl-amine
17.18	trans-Ethyl-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	447	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester	Morpholine
17.19	trans-Benzyl-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	509	trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	Morpholine

17.20	trans-Methyl-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	433	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester	Morpholine
17.21	trans-Allyl-[4-(6-morpholin-4-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	459	trans-Allyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	Morpholine
17.22	trans-[4-(6-Morpholin-4-yl-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	563	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	Morpholine
17.23	trans-Ethyl-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	431	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester	Pyrrolidine
17.24	trans-Benzyl-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	493	trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	Pyrrolidine
17.25	trans-Methyl-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	417	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester	Pyrrolidine
17.26	trans-Allyl-[4-(6-pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	443	trans-Allyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	Pyrrolidine

17.27	[4-(6-Pyrrolidin-1-yl-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	547	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	Pyrrolidine

Example 18

1 eq of the bromide (0.13mmol bromide/1ml DMF) is treated with 3 eq of amine in the presence of 1 eq diisopropylethylamine and a catalytic amount of NaI at RT until no starting material can be detected with HPLC. Formic acid is added and the crude materials are purified by prep HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile]. After purification, the product is extractet with EtOAc and sat. $NaHCO_3/H_2O$ to isolate the free amine. The following compounds were prepared from the corresponding bromides and amines:

Example	Compound	MS MH^+	Bromide	Amine
18.1	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid benzyl ester	417	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester	N-Allylmethyl-amine
18.2	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-ethyl-carbamic acid benzyl ester	431	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester	N-Allylmethyl-amine
18.3	trans-Allyl-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-carbamic acid benzyl ester	443	trans-Allyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	N-Allylmethyl-amine
18.4	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-benzyl-carbamic acid benzyl ester	493	trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	N-Allylmethyl-amine
18.5	trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	547	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	N-Allylmethyl-amine

18.6	trans-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester	391	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester	Dimethylamine 33% in EtOH 5.6M
18.7	trans-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester	405	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester	Dimethylamine 33% in EtOH 5.6M
18.8	trans-Allyl-[4-(6-dimethylamino-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	417	trans-Allyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	Dimethylamine 33% in EtOH 5.6M
18.9	trans-Benzyl-[4-(6-dimethylamino-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	467	trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester	Dimethylamine 33% in EtOH 5.6M
18.10	trans-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	521	trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester	Dimethylamine 33% in EtOH 5.6M

Example 19

19.1

In analogy to example 17, trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid benzyl ester, MS: 435 (MH^+), was obtained from trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-methyl-carbamic acid benzyl ester and N-(2-Methoxyethyl)methylamine.

19.2

Hydrogenation of 0.43 g (0.001 mmol) trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid benzyl ester in 4 ml EtOAc in the presence of 0.06 g 10%Pd /C for 1h yielded after removal of the catalyst and evaporation of the solvent 0.29 g (98%) trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-amine as colorless oil, MS: 301 (MH^+).

19.3

In analogy to examples 19.1 and 19.2, trans-Ethyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-amine, MS: 315 (MH^+), was obtained from trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-ethyl-carbamic acid benzyl ester and N-(2-Methoxyethyl)-methylamine.

19.4

In analogy to examples 19.1 and 19.2, trans-Benzyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-amine, MS: 377 (MH^+), was obtained from trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester and N-(2-Methoxyethyl)-methylamine.

19.5

In analogy to examples 19.1 and 19.2, trans-4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexylamine, MS: 287 (MH^+), was obtained from trans-Benzyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester and N-(2-Methoxyethyl)-methylamine (hydrogenation over night).

19.6

In analogy to examples 19.1 and 19.2, trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-amine, MS: 431 (MH^+), was obtained from trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-(2,4,5-trifluoro-benzyl)-carbamic acid benzyl ester and N-(2-Methoxyethyl)methylamine.

19.7

In analogy to examples 19.1 and 19.2, trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-propyl-amine, MS: 329 (MH^+), was obtained from trans-Allyl-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester and N-(2-Methoxyethyl)-methylamine.

Example 20

1 eq of the amine is treated with sulfonylchloride (1.1 eq for each NH_2) in (2-5 ml/mmol amine) dioxane in the presence of 1.1 eq of diisopropylamine at RT until no starting material can be detected with TLC. The solutions are diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4. Flash chromatography or purification by prep HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile] followed by extraction with EtOAc and sat. $NaHCO_3/H_2O$ yields the free amines. The following compounds were prepared from the corresponding amines and sulfonylchlorides:

Example	Compound	MS MH^+	Amine	Sulfonylchloride
20.1	trans-4-Chloro-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-methyl-benzenesulfonamide	475 (1 Cl)	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-amine	4-Chlorobenzene-sulfonylchloride
20.2	trans-4-Chloro-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-benzenesulfonamide	461 (1 Cl)	trans-4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexylamine	4-Chlorobenzene-sulfonylchloride
20.3	trans-4-Bromo-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-benzenesulfonamide	505 (1 Br)	trans-4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexylamine	4-Bromobenzene-sulfonylchloride
20.4	trans-4-Chloro-N-ethyl-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-benzenesulfonamide	489 (1 Cl)	trans-Ethyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-amine	4-Chlorobenzene-sulfonylchloride

20.5	trans-4-Bromo-N-ethyl-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-benzenesulfonamide	533 (1 Br)	trans-Ethyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-amine	4-Bromobenzene-sulfonylchloride
20.6	trans-4-Chloro-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-propyl-benzenesulfonamide	503 (1 Cl)	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-propyl-amine	4-Chlorobenzene-sulfonylchloride
20.7	trans-4-Bromo-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-propyl-benzenesulfonamide	547 (1 Br)	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-propyl-amine	4-Bromobenzene-sulfonylchloride
20.8	trans-4-Chloro-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-(2,4,5-trifluoro-benzyl)-benzenesulfonamide	605 (1 Cl)	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-amine	4-Chlorobenzene-sulfonylchloride
20.9	trans-4-Bromo-N-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-N-(2,4,5-trifluoro-benzyl)-benzenesulfonamide	649 (1 Br)	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-amine	4-Bromobenzene-sulfonylchloride

Example 21

1 eq of the amine is treated with chloroformate (1.1 eq for each NH_2) in (2-5 ml/mmol amine) dioxane in the presence of 1.1 eq of diisopropylamine at RT until no starting material can be detected with TLC. The solutions are diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4. Flash chromatography or purification by prep HPLC [RP-18, acetonitrile (0.1 % HCOOH)/water (0.1 % HCOOH), 10 % to 95 % acetonitrile] followed by extraction with EtOAc and sat. $NaHCO_3/H_2O$ yields the free amines. The following compounds were prepared from the corresponding amines and chloroformates:

Example	Compound	MS MH^+	Amine	Chloroformate
21.1	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester	455 (1 Cl)	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyl-oxy}-cyclohexyl)-methyl-amine	4-Chlorophenyl-chloroformate
21.2	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid 4-chloro-phenyl ester	441 (1 Cl)	trans-4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexylamine	4-Chlorophenyl-chloroformate
21.3	trans-Ethyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-carbamic acid 4-chloro-phenyl ester	469 (1 Cl)	trans-Ethyl-(4-{6-[(2-methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-amine	4-Chlorophenyl-chloroformate
21.4	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-propyl-carbamic acid 4-chloro-phenyl ester	483 (1 Cl)	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyl-oxy}-cyclohexyl)-propyl-amine	4-Chlorophenyl-chloroformate

21.5	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyloxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-carbamic acid 4-chloro-phenyl ester	585 (1 Cl)	trans-(4-{6-[(2-Methoxy-ethyl)-methyl-amino]-hexyl-oxy}-cyclohexyl)-(2,4,5-trifluoro-benzyl)-amine	4-Chlorophenyl-chloroformate

Example 22

22.1

To 15.0 g (60 mmol) trans-4-Hydroxy-cyclohexylcarbamic acid benzyl ester suspended in 183 ml (1.2 mol, 20 eq) 1,6-Dibromohexane, 6.1 g (18 mmol, 0.3 eq) tetrabutyl-ammoniumhydrogensulfate and 183 ml 50% aqueous NaOH were added. The mixture was stirred at RT for 4 days, CH_2Cl_2 was added and the layers were separated. The inorganic layer was extracted with CH_2Cl_2, the combined organic layers were washed with brine and dried over Na_2SO_4. The excess of dibromide was removed in vacuo and the residue was purified by column chromatography on silica gel with hexane:EtOAc 1:1 as eluent yielding 3.4 g (14%) trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester as white solid, MS: 412 (MH^+, 1Br) and 11.2 g (32%) trans-(6-Bromo-hexyl)-[4-(6-bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester as yellow oil, MS: 575 (MH^+, 1Br).

22.2

In analogy to example 22.1, trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-carbamic acid benzyl ester was obtained as white solid, MS: 398 (MH^+, 1Br), from trans-4-Hydroxy-cyclohexylcarbamic acid benzyl ester and 1,5-Dibromopentane.

22.3

1.7 g (4.12 mmol) trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester in DMA were treated with 2.2 ml 5.6M (12.4 mmol, 3eq) dimethylamine in ethanol. The solution was stirred at RT over night, concentrated and the residue was redissolved in CH_2Cl_2/ 5% aqueous Na_2CO_3, the phases were separated and the inorganic phase was extracted with CH_2Cl_2, the combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified over silica gel with CH_2Cl_2:MeOH 9:1 yielding 1.3 g (84%) trans-[4-(6-Dimethylamino-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester as light yellow solid, MS: 377 (MH^+).

22.4

In analogy to example 22.3, trans-[4-(5-Dimethylamino-pentyloxy)-cyclohexyl]-carbamic acid benzyl ester was obtained as light yellow solid, MS: 363 (MH^+), from trans-[4-(5-Bromo-pentyloxy)-cyclohexyl]-carbamic acid benzyl ester and dimethylamine.

22.5

In analogy to example 22.3, trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-carbamic acid benzyl ester was obtained as off-white solid, MS: 377 (MH^+), from trans-[4-(6-Bromo-hexyloxy)-cyclohexyl]-carbamic acid benzyl ester and N-allylmethylamine.

Example 23

23.1

30 g (123.3mmol) BOC-trans-1,4-amino cyclo-hexane carboxylic acid and 22 g (135.6 mmol) Carbonyl-di-imidazol were dissolved in 300ml THF and stirred at RT for 30 min. 50 ml(1.23 mol) of methanol were added and the solution was refluxed for 3h. The solution was evaporated under reduced pressure, dissolved in ether and washed with 1N HCl and water. The ether-phase was concentrated in vacuum to yield 31.7 g 4-trans-4-tert-Butoxy carbonylamino-cyclohexane carboxylic acid methyl ester, MS: 275.4($M+NH_4^+$).

23.2

A solution of 1.52 g (40 mmol) LAH in 7 ml THF was refluxed and treated for 2.5 h with a solution of 5.15 g (20 mmol) of trans-4-tert-butoxycarbonylamino-cyclohexanecarboxylic acid methyl ester in 35 ml THF. The reaction was heated for 15 h, cooled (0 °C) and hydrolyzed with 10 ml water. The mixture was diluted with THF, dried over Na_2SO_4, filtered and evaporated. The residue was dissolved in CH_2Cl_2, dried over Na_2SO_4, filtered and evaporated to yield 2.89 g (100 %) of trans-(4-Methylamino-cyclohexyl)-methanol, mp: 87-88 °C; MS: 143 (M).

23.3

A solution of 1.00 g (7 mmol) of (trans)-(4-Methylamino-cyclohexyl)-methanol in 20 ml pyridine was treated at 0 °C with 1.80 (7.35 mmol) 4-(trifluoromethyl)-benzenesulfonyl chloride. The reaction was stirred 40 min at 0 °C and poured on ice-water. Acidification (25 % HCl), extraction (Et_2O, 3x) and drying of the organic phase over Na_2SO_4 yielded after evaporation and flash column chromatography on silica gel with CH_2Cl_2/MeOH (99:1 to 98:2) 0.71 g (18 %) trans-4-Trifluoromethyl-benzenesulfonic acid 4-[methyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-cyclohexylmethyl ester, MS: 560 (MH^+), and 0.68 (28 %) of trans-N-(4-Hydroxymethyl-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide, MS: 352 (MH^+).

23.4

4.60 g (32.14 mmol) of trans-(4-Methylamino-cyclohexyl)-methanol 69-5651 was suspended in 85 ml hexamethyldisilazane and refluxed for 5 h. The solution was evaporated under reduced pressure and dissolved in 50 ml THF. 6.14 g (32.14 mmol) of 4-chlorophenylchloroformate were added slowly at 0 °C and stirred for 16 h at room temperature. 30 ml H_2O were added and after 1h the solvents were evaporated. The residue was extracted with water/Et_2O (3x), the organic phases were washed with 10% NaCl, dried over Na_2SO_4 and evaporated to yield after flash-chromatography on silica gel

(hexane/EtOAc 4:1 to 1:1) 5.48 g (57 %) of trans-(4-Hydroxymethyl-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester, MS: 298 (MH^+, 1Cl).

23.5

A solution of 0.6 g (2.03 mmol) of trans-(4-Hydroxymethyl-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester in 15 ml CH_2Cl_2 was treated with 0.17 ml (2.24 mmol) methanesulfonylchloride, 0.5 ml (6.1 mmol) pyridine and 0.25 g (2.03 mmol) DMAP at 0 °C. The reaction mixture was warmed up over night to room temperature, water (2 ml) was added and the reaction mixture was stirred for 5 min. After extraction with aqueous 10% $KHSO_4/Et_2O$ (3x), the organic phases were washed with aqueous $KHCO_3$ (2x), aqueous 10% NaCl, dried over Na_2SO_4 and evaporated to yield 0.74 g (96 %) of trans-Methanesulfonic acid 4-[(4-chloro-phenoxycarbonyl)-methyl-amino]-cyclohexylmethyl ester, mp: 134-135 °C; MS: 376 (MH^+, 1 Cl).

23.6

[following a procedure of Belostotskii, Anatoly M.; Hassner, Alfred. Synthetic methods. 41. Etherification of hydroxysteroids via triflates. Tetrahedron Lett. (1994), 35(28), 5075-6.]. A solution of 0.175 ml (2 mmol) 3-bromo-1-propanol and 0.48 ml 2,6-di-tert-butylpyridine in 1 ml CH_2Cl_2 was treated at 0 °C with a solution of 0.35 ml (2.1 mmol) trifluoromethansulfonic anhydride in 0.5 ml CH_2Cl_2. After 2.5 h at 0 °C, the violet solution was evaporated, dissolved in 1 ml nitromethane and treated with a solution of 0.375 g (1 mmol) trans-N-(4-Hydroxymethyl-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide and 0.45 ml (2 mmol) 2,6-di-tert-butylpyridine in 3 ml nitromethane (during 3 min). The reaction was heated (60 °C) for 3.5 h and then extracted with aqueous 10% $KHSO_4$/EtOAc (3x). The organic phases were washed with aqueous saturated $NaHCO_3$, aqueous 10% NaCl, dried over Na_2SO_4 and evaporated. Purification by flash-chromatography on silica gel (hexane/EtOAc 9:1) yielded 0.3 g (64%) of trans-N-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide, MS: 452 (M-F, 1Br).

23.7

In analogy to example 23.6, trans-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester, MS: 418 (MH^+, 1Br, 1Cl) was obtained from trans-(4-Hydroxymethyl-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester and 3-bromo-1-propanol.

23.8

In analogy to example 23.6, trans-[4-(2-Bromo-ethoxymethyl)-cyclohexyl]-methyl-

carbamic acid 4-chloro-phenyl ester, MS: 404 (MH^+, 1Br, 1Cl) was obtained from trans-(4-Hydroxymethyl-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester and 2-bromoethanol.

23.9

A solution of 1.5 g (5.04 mmol) of trans-(4-Hydroxymethyl-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl in 30 ml of DMF was treated with 1.19 ml (15.11 mmol) of 1,4-dibromobutane and at 0 °C with 0.28 g (5.79 mmol) of 55% NaH in small portions. The reaction was stirred for 16 h at RT. The reaction was treated again with 1.19 ml (15.11 mmol) of 1,4-dibromobutane and at 0 °C with 0.28 g (5.79 mmol) of 55% NaH in small portions and stirred for 3 days at RT. The solution was then poured into cooled aqueous saturated NH_4Cl and extracted (Et_2O 3x). The organic phase was washed with water, dried over Na_2SO_4, evaporated and purified by flash silica gel column (first with hexane to remove the dibromobutane and then Hexane/ EtOAc 4:1 to 1:1) to yield 0.59 g (27 %) of trans-[4-(4-Bromo-butoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester, MS: 432 (MH^+, 1Br, 1Cl).

23.10

A solution of 69 mg (0.146 mmol) of trans-N-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide in 0.8 ml DMA was treated at 0 °C with 0.028 ml (0.29 mmol) of N-allylmethylamine and stirred at RT for 22h. The solution was cooled (0 °C) and treated again with 0.028 ml (0.29 mmol) of N-allylmethylamine. After 6 h at RT, the solution was concentrated and dissolved in aqueous saturated $NaHCO_3$ /Et_2O (3x). The organic phase was dried over Na_2SO_4 and evaporated. Flash column chromatography on silica gel with CH_2Cl_2/MeOH (95:5) yielded 43 mg (64 %) of trans-N-{4-[3-(Allyl-methyl-amino)-propoxymethyl]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide, MS: 463 (MH^+).

23.11

In analogy to example 23.10, trans-N-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide, MS: 481 (MH^+), was obtained from trans-N-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide and 2-ethylaminoehanol.

23.12

In analogy to example 23.10, trans-N-[4-(3-Azetidin-1-yl-propoxymethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide, MS: 449 (MH^+), was obtained from trans-

N-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide and trimethylenimine.

23.13

In analogy to example 23.10, trans-N-Methyl-N-[4-(3-piperidin-1-yl-propoxymethyl)-cyclohexyl]-4-trifluoromethyl-benzenesulfonamide, MS: 477 (MH^+), was obtained from trans-N-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide and piperidine.

23.14

In analogy to example 23.10, trans-{4-[3-(Allyl-methyl-amino)-propoxymethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester, MS: 409 (MH^+, 1Cl) was obtained from trans-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and N-allylmethylamine.

23.15

In analogy to example 23.10, trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propoxymethyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester, MS: 427 (MH^+, 1Cl) was obtained from trans-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and 2-ethylaminoethanol.

23.16

In analogy to example 23.10, trans-[4-(3-Azetidin-1-yl-propoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester, MS: 395 (MH^+, 1Cl) was obtained from trans-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and trimethylenimine.

23.17

In analogy to example 23.10, trans-Methyl-[4-(3-piperidin-1-yl-propoxymethyl)-cyclohexyl]-carbamic acid 4-chloro-phenyl ester, MS: 423 (MH^+, 1Cl) was obtained from trans-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and piperidine.

23.18

In analogy to example 23.10, trans-(4-{3-[Ethyl-(2-methoxy-ethyl)-amino]-propoxymethyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester, MS: 441 (MH^+, 1Cl) was obtained from trans-[4-(3-Bromo-propoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and N-(2-methoxyethyl)ethylamine.

23.19

In analogy to example 23.10, trans-{4-[4-(Allyl-methyl-amino)-butoxymethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester, MS: 423 (MH^+, 1Cl) was obtained from trans-[4-(4-Bromo-butoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and N-allylmethylamine.

23.20

In analogy to example 23.10, trans-{4-[2-(Allyl-methyl-amino)-ethoxymethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester, MS: 395 (MH^+, 1Cl) was obtained from trans-[4-(2-Bromo-ethoxymethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and N-allylmethylamine.

Example 24

24.1

5.53 g (20 mmol) triphenylmethanethiol in 50 ml DMA were deprotonated at 0 °C with 0.87 g (20 mmol) of 55% NaH. The reaction was stirred for 30 min at RT, dropped slowly (30 min) to a cooled (0 °C) solution of 1.72 ml (20 mmol) of 1,2-dibromoethane in 50 ml DMA. The reaction mixture was stirred for 6 h at RT, cooled (0 °C) and treated with 3.83 ml (40 mmol) of N-allylmethylamine. After 16 h at RT, the reaction was cooled (0 °C) and treated again with 3.83 ml (40 mmol) of N-allylmethylamine. After 24 h at RT, the solution was concentrated and dissolved in aqueous saturated $NaHCO_3$ /Et_2O (3x). The organic phase was dried over Na_2SO_4 and evaporated. Flash column chromatography on silica gel with CH_2Cl_2/MeOH (99.5:0.5 to 95:5) yielded 3.27 (44 %) of Allyl-methyl-(2-tritylsulfanyl-ethyl)-amine, MS: 374 (MH^+).

24.2

A solution of 1.12 g (3 mmol) of Allyl-methyl-(2-tritylsulfanyl-ethyl)-amine in 30 ml CH_2Cl_2 was treated at 0 °C with 8.7 ml TFA followed by 6.15 ml (30 mmol) triisopropylsilane. After 30 min at RT, the reaction mixture was evaporated, dissolved in toluene (3x) and evaporated. The TFA-salt was precipitated from ether/pentane. The oil was dissolved in ether, washed with aqueous saturated $NaHCO_3$, aqueous 10% NaCl, dried over Na_2SO_4 and evaporated carefully to yield 0.366 g (93 %) of 2-(Allyl-methyl-amino)-ethanethiol, MS: 132 (MH^+).

24.3

In analogy to examples 24.1 and 24.2, N-Allylmethylamine and 1,3-dibrompropane were converted to 3-(Allyl-methyl-amino)-propane-1-thiol, MS: 145 (MH^+).

24.4

A solution of 280 mg (0.5 mmol) of trans-4-Trifluoromethyl-benzenesulfonic acid 4-[methyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-cyclohexylmethyl ester and 78 mg (0.55 mmol) of 2-dimethylaminoethanethiol hydrochloride in 4.5 ml DMF was treated at 0 °C with 48 mg (1.1 mmol) of 55% NaH, stirred for 20 h at RT. After cooling (0 °C) and treatment with a catalytic amount of NaI followed by 78 mg (0.55 mmol) of 2-dimethylaminoethanethiol hydrochloride and 48 mg (1.1 mmol) of 55% NaH the reaction mixture was stirred for 18 h at RT. The reaction was neutralized (aqueous 10% $KHSO_4$, at 0 °C) and poured into aqueous sat. $NaHCO_3$/Et_2O (3x). The organic phases were washed with aqueous 10% NaCl solution, dried over Na_2SO_4 and evaporated. Purification by flash column chromatography on silica gel with CH_2Cl_2/MeOH (95:5) yielded 138 mg (63 %) of

trans-N-[4-(2-Dimethylamino-ethylsulfanylmethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide, MS: 439 (MH^+).

24.5

In analogy to example 24.4, trans-4-Trifluoromethyl-benzenesulfonic acid 4-[methyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-cyclohexylmethyl ester and 2-(allyl-methyl-amino)-ethanethiol were converted to trans-N-{4-[2-(Allyl-methyl-amino)-ethylsulfanylmethyl]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide, MS: 465 (MH^+),

24.6

In analogy to example 24.4, trans-4-Trifluoromethyl-benzenesulfonic acid 4-[methyl-(4-trifluoromethyl-benzenesulfonyl)-amino]-cyclohexylmethyl ester and 2-diethylaminoethanethiol hydrochloride with an excess of NaH were converted to trans-N-[4-(2-Diethylamino-ethylsulfanylmethyl)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide, MS: 467 (MH^+),

24.7

In analogy to example 24.4, trans-Methanesulfonic acid 4-[(4-chloro-phenoxycarbonyl)-methyl-amino]-cyclohexylmethyl ester and 2-diethylaminoethanethiol hydrochloride with an excess of NaH were converted to trans-[4-(2-Diethylamino-ethylsulfanylmethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester, MS: 413 (MH^+, 1Cl),

24.8

In analogy to example 24.4, trans-Methanesulfonic acid 4-[(4-chloro-phenoxycarbonyl)-methyl-amino]-cyclohexylmethyl ester and 2-(allyl-methyl-amino)-ethanethiol were converted to trans-{4-[2-(Allyl-methyl-amino)-ethylsulfanylmethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester, MS: 411 (MH^+, 1Cl),

24.9

In analogy to example 24.4, trans-Methanesulfonic acid 4-[(4-chloro-phenoxycarbonyl)-methyl-amino]-cyclohexylmethyl ester and 3-(allyl-methyl-amino)-propane-1-thiol were converted to trans-{4-[3-(Allyl-methyl-amino)-propylsulfanylmethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester, MS: 425 (MH^+, 1Cl),

24.10

In analogy to example 24.4, trans-Methanesulfonic acid 4-[(4-chloro-phenoxycarbonyl)-methyl-amino]-cyclohexylmethyl ester and 2-(dimethylamino)-ethane-1-thiol were

converted to trans-[4-(2-Dimethylamino-ethylsulfanylmethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester, MS: 385 (MH^+, 1Cl).

Example 25

25.1

To 1.72 g (4.58 mmol) trans-Methanesulfonic acid 4-[(4-chloro-phenoxycarbonyl)-methyl-amino]-cyclohexylmethyl ester in 17 ml DMF, 0.78 g (6.86 mmol, 1.5 eq) potassium thioacetate were added and the mixture was heated to 100 °C for 10 min. The mixture was concentrated under vacuum and the residue was dissolved in saturated $NaHCO_3/Et_2O$(3x). The organic phases were washed with brine, dried over Na_2SO_4 and evaporated to yield 1.69 g (quantitative) of trans-Thioacetic acid S-{4-[(4-chloro-phenoxycarbonyl)-methyl-amino]-cyclohexylmethyl} ester, MS: 356 (MH^+).

25.2

A solution of 0.63 g (corresponds to 1.7 mmol) crude trans-Thioacetic acid S-{4-[(4-chloro-phenoxycarbonyl)-methyl-amino]-cyclohexylmethyl} ester in 20 ml degassed (Ar) ethanol was treated with 5.1 ml 1N LiOH and 10 min later with 0.5 ml (6.8 mmol) 2-bromo-ethanol. The reaction mixture was stirred for 1.25 h, cooled (0 °C) and neutralized with aqueous 10% $KHSO_4/Et_2O$ (3x). The organic phases were washed with aqueous 10% NaCl and dried over Na_2SO_4 to yield after evaporation with toluene 0.67 g (quantitative) trans-[4-(2-Hydroxy-ethylsulfanylmethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester, MS: 358 (MH^+, 1Cl).

25.3

A solution of 645 mg (corresponds to 1.65 mmol) of trans-[4-(2-Hydroxy-ethylsulfanylmethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester in 12 ml CH_2Cl_2 was treated at 0 °C with 0.14 ml (1.82 mmol) methanesulfonylchloride, 0.20 ml (2.45 mmol) pyridine and 202 mg (1.65 mmol) DMAP. The reaction mixture was warmed up over night to room temperature. Water (2 ml) was added and the reaction was stirred for 5 min. After extraction with aqueous 10% $KHSO_4/Et_2O$ (3x), the organic phases were washed with aqueous saturated $KHCO_3$ (2x), aqueous 10% NaCl, dried over Na_2SO_4 and evaporated to yield 650 mg (quantitative) trans-[4-(2-Chloro-ethylsulfanylmethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester, MS: 376 (MH^+, 2Cl).

25.4

A solution of 94 mg (0.25 mmol) of trans-[4-(2-Chloro-ethylsulfanylmethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester in 1 ml DMA was treated with a catalytic amount of NaI and with 0.05 ml (0.5 mmol) of 2-ethylaminoethanol and stirred at RT for 16 h. The reaction mixture was stirred for 1 week, adding every day twice 0.05 ml (0.5 mmol) of 2-ethylaminoethanol. The solution was concentrated and the residual oil was

extracted with aqueous sat. $NaHCO_3/Et_2O$ (3x). The organic phases were washed with aqueous 10% NaCl solution and dried over Na_2SO_4 to yield after flash column chromatography on silica gel (CH_2Cl_2/MeOH 95:5) 40 mg (39 %) of trans-(4-{2-[Ethyl-(2-hydroxy-ethyl)-amino]-ethylsulfanylmethyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester, MS: 429 (MH^+, 1Cl).

25.5

In analogy to example 25.4, trans-[4-(2-Chloro-ethylsulfanylmethyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and N-methylpropylamine were converted to trans-Methyl-{4-[2-(methyl-propyl-amino)-ethylsulfanylmethyl]-cyclohexyl}-carbamic acid 4-chloro-phenyl ester, MS: 429 (MH^+, 1Cl).

Example 26

26.1

A solution of 20 g (82.2 mmol) trans-4-tert-Butoxycarbonylamino-cyclohexanecarboxylic acid in 1.2 l CH_2Cl_2 was treated with 12.83 g (131.5 mmol) N,O-dimethyl-hydroxylamine hydrochloride, 10.85 ml (98.6 mmol) N-methylmorpholine and at 0 °C with 18.91 g (98.64 mmol) EDCI and 12.62 g (82.2 mmol) HOBT. The reaction mixture was stirred 2 h at room temperature and extracted with aqueous 10% $KHSO_4$/Et_2O (3x). The organic phases were washed with aqueous saturated $NaHCO_3$, 10% NaCl and dried over Na_2SO_4 to yield 24.25 g (quantitative) trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-carbamic acid tert-butyl ester, mp: 130-140 °C, slowly dec.; MS: 287 (MH^+).

26.2

A solution of 24.18 g (82 mmol) of trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-carbamic acid tert-butyl ester in 80 ml of DMF was treated at 0 °C with 5.37 g (123 mmol) of 55% NaH in small portions. The reaction was stirred for 1 h at 0 °C, then treated slowly (20 min) with 40.9 ml (656 mmol) iodomethane and warmed up to RT over night. The reaction is cooled and neutralized with aqueous 10% $KHSO_4$ and poured into water/Et_2O (3x). The organic phase was washed with aqueous 10% NaCl, dried over Na_2SO_4 evaporated and purified by flash silica gel column (CH_2Cl_2/ EtOAc 9:1 to 1:1) to yield 20.69 g (84 %) of trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, MS: 301 (MH^+).

26.3

A solution of 2.09 g (55 mmol) LAH in 250 ml THF was cooled (-50 °C) and treated during 25 min with a solution of 15.02 g (50 mmol) of trans-[4-(Methoxy-methyl-carbamoyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester in 250 ml THF. The reaction was warmed up to +15 °C for 3.5 h, cooled (-78 °C) and hydrolyzed with a suspension of 15 g $MgSO_4.7H_2O$, 15 g silicagel in 50 ml aqueous 10% $KHSO_4$. The cooling bath was removed, THF was added, the mixture was stirred for 30 min and filtered. After evaporation, the residue was dissolved in CH_2Cl_2, dried over Na_2SO_4 and evaporated to yield 12.83 (quantitative) trans-(4-Formyl-cyclohexyl)-methyl-carbamic acid tert-butyl ester, MS: 241 (M).

26.4

A solution of 52.45 g (200 mmol) triphenylphosphine in 200 ml CH_2Cl_2 was treated with 33.16 g (100 mmol) tetrabromomethane (the reaction heated up to reflux) and after 50 min with 32.06 ml (230 mmol) triethylamine (the reaction heated up to reflux and became

dark violet). After cooling (0 °C), 12.83 g (50 mmol) of trans-(4-Formyl-cyclohexyl)-methyl-carbamic acid tert-butyl ester in 125 ml CH_2Cl_2 were added during 10 min. The solution was stirred for 16 h at RT, evaporated and filtered through silica gel (deactivated with hexane/Et_3N) with hexane and then hexane/ether 4:1 to 1:1 as eluent to yield 13.28 g (67 %) of trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, mp: 93-99 °C, dec.; MS: 396 (MH^+, 2Br).

26.5

The following reaction was performed in analogy to the reaction described in: Marshall, James A.; Bartley, Gary S.; Wallace, Eli M. Total Synthesis of the Pseudopterane (-)-Kallolide B, the Enantiomer of Natural (+)-Kallolide B. J. Org. Chem. (1996), 61(17), 5729-5735 and Baker, Raymond; Boyes, Alastair L.; Swain, Christopher J. Synthesis of talaromycins A, B, C, and E. J. Chem. Soc., Perkin Trans. 1 (1990), (5), 1415-21.). A solution of 993 mg (2.5 mmol) of trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester in 20 ml THF was treated at -78 °C with 3.28 ml (5.25 mmol) of BuLi (ca 1.6 M in hexane). After 2 h at this temperature 790 mg (25 mmol) of paraformaldehyde were added. The reaction mixture was warmed up to RT for 3h and after 1 h at this temperature extracted with water/ether (3x). The organic phases were washed with aqueous 10% NaCl, dried over Na_2SO_4 and evaporated. Purification by flash-chromatography on silica gel (hexane/EtOAc 4:1) yielded 530 g (79 %) of trans-[4-(3-Hydroxy-prop-1-ynyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, MS: 268 (MH^+).

26.6

A solution of 3.97 g (10 mmol) of trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester in 160 ml THF was treated at -78 °C with 13.13 ml (21 mmol) of BuLi (ca 1.6 M in hexane) and stirred for 2h. 11 ml DMPU were added and 10 min later 4.60 g (20 mmol) of 1-bromo-3-tetrahydropyranyloxypropane in 15 ml THF were added over a period of 20 min. The reaction mixture was warmed up to RT for 16 h, cooled, poured into cooled aqueous saturated NH_4Cl and extracted (Et_2O 3x). The organic phase was washed with aqueous 10% NaCl, water, dried over Na_2SO_4, evaporated and purified by flash silica gel column (Hexane/ EtOAc 98:2 to 90:10) to yield 1.61 g (42 %) of trans-Methyl-{4-[5-(tetrahydro-pyran-2-yloxy)-pent-1-ynyl]-cyclohexyl}-carbamic acid tert-butyl ester, MS: 378 (M-H).

26.7

A solution of 520 mg (1.95 mmol) of trans-[4-(3-Hydroxy-prop-1-ynyl)-cyclohexyl]-

methyl-carbamic acid tert-butyl ester in 14 ml CH_2Cl_2 was treated at 0 °C with 0.17 ml (2.14 mmol) methanesulfonylchloride, 0.235 ml (2.92 mmol) pyridine and 238 mg (1.95 mmol) DMAP. The reaction mixture was warmed up over night to room temperature, water (2 ml) was added and the reaction was stirred for 5 min. After extraction with aqueous 10% $KHSO_4/Et_2O$ (3x) the organic phases were washed with aqueous $KHCO_3$ (2x), aqueous 10% NaCl, dried over Na_2SO_4 and evaporated to yield 435 mg (65 %) of trans-Methanesulfonic acid 3-[4-(tert-butoxycarbonyl-methyl-amino)-cyclohexyl]-prop-2-ynyl ester, MS: 345 (M).

26.8

A solution of 420 mg (1.22 mmol) of trans-Methanesulfonic acid 3-[4-(tert-butoxycarbonyl-methyl-amino)-cyclohexyl]-prop-2-ynyl ester in 4 ml DMA was treated at 0 °C with 0.234 ml (2.43 mmol) of N-allylmethylamine and stirred at RT for 16 h. The solution was concentrated and the residual oil was extracted with aqueous sat. $NaHCO_3/Et_2O$ (3x). The organic phases were washed with aqueous 10% NaCl solution and dried over Na_2SO_4 to yield after flash column chromatography on silica gel with hexane/EtOAc (2:1) 355 mg (91 %) trans-{4-[3-(Allyl-methyl-amino)-prop-1-ynyl]-cyclohexyl}-methyl-carbamic acid tert-butyl ester, MS: 321 (MH^+).

26.9

A solution of 200 mg (0.62 mmol) of trans-{4-[3-(Allyl-methyl-amino)-prop-1-ynyl]-cyclohexyl}-methyl-carbamic acid tert-butyl ester in 3.5 ml CH_2Cl_2 was treated at 0 °C with 1.7 ml TFA (for 20 min). After 30 min at this temperature, the reaction mixture was evaporated, treated with 1 N NaOH/ CH_2Cl_2 (3x). The organic phase was dried over Na_2SO_4 and evaporated to yield 147 mg (quantitative) of trans-{4-[3-(Allyl-methyl-amino)-prop-1-ynyl]-cyclohexyl}-methyl-amine, MS: 221 (MH^+).

26.10

A solution of 66 mg (0.3 mmol) of trans-{4-[3-(Allyl-methyl-amino)-prop-1-ynyl]-cyclohexyl}-methyl-amine in 0.3 ml dioxane was treated with 0.103 ml (0.6 mmol; 2 equivalents) Huenig's base and dropwise with a solution of 0.042 ml (0.27 mmol) 4-chlorophenylchloroformate in 0.16 ml dioxane (during 10 min). After 5 min at RT, the mixture was dissolved in aqueous saturated $NaHCO_3$ /Et_2O (3x). The organic phase was dried over Na_2SO_4 and evaporated. Flash column chromatography on silica gel with CH_2Cl_2/MeOH (99:1 to 97:3) yielded 68 mg (61 %) of trans-{4-[3-(Allyl-methyl-amino)-prop-1-ynyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester, MS: 375 (MH^+, 1Cl).

Example 27

27.1

A solution of 975 mg (3.28 mmol) of trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester in 20 ml CH_2Cl_2 was treated at 0 °C with 10 ml TFA (for 20 min). After 2 h at RT, the reaction was evaporated, treated with aqueous saturated $NaHCO_3(+Na_2CO_3)/Et_2O$ (3x), dried over Na_2SO_4 and evaporated to yield 981 mg (87 %) of trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-amine, MS: 295 (M, 2Br).

27.2

In analogy to example 26.10 trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-amine and 4-chlorophenylchloroformate were converted to trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester, MS: 449 (M, 2Br, 1 Cl),

27.3

In analogy to example 26.5, trans-[4-(2,2-Dibromo-vinyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and BuLi (ca 1.6 M in hexane) with paraformaldehyde were converted to trans-[4-(3-Hydroxy-prop-1-ynyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester, MS: 321 (M, 1Cl),

27.4

In analogy to example 26.7, trans-[4-(3-Hydroxy-prop-1-ynyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and methanesulfonylchloride/pyridine were converted to trans-Methanesulfonic acid 3-{4-[(4-chloro-phenoxycarbonyl)-methyl-amino]-cyclohexyl}-prop-2-ynyl ester, MS: 400 (MH^+, 1Cl),

27.5

In analogy to example 26.8, trans-Methanesulfonic acid 3-{4-[(4-chloro-phenoxycarbonyl)-methyl-amino]-cyclohexyl}-prop-2-ynyl ester and 2-ethylaminoethanol were converted to trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-prop-1-ynyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester, MS: 393 (MH^+, 1Cl),

Example 28

28.1

A suspension of 65 mg (0.165 mmol) of trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-prop-1-ynyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester 71-5038 in 5 ml MeOH and 7 mg Pt/C 10% was hydrogenated (1 atm) for 16 h. The reaction was filtered (Celite) and evaporated. Flash column chromatography on silica gel with CH_2Cl_2/MeOH (9:1) gave 21 mg (32 %) of of trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester, MS: 397 (MH^+, 1Cl).

Example 29

29.1

16.2 g (62.95 mmol) of 4-trans-4-tert-Butoxy carbonylamino-cyclohexane carboxylic acid methyl ester and 5.87 ml (94.43 mmol) of methyl iodid in 100ml DMF were treated under stirring and ice-cooling with 3.57 g (81.84 mmol) of NaH (55% in oil). The solution was stirred at RT for 20h and then treated under ice-cooling with 1N HCl. The reaction-mixture was dissolved in ether and washed 4 times with water. The ether-phases were concentrated in vacuum to yield 17.5 g of clean trans-4-(tert-Butoxycarbonyl-methyl-amino)-cyclohexanecarboxylic acid methyl ester, MS: 201.

29.2

17.1 g (62.95 mmol) of trans-4-(tert-Butoxycarbonyl-methyl-amino)-cyclohexanecarboxylic acid methyl ester, dissolved in 150 ml of THF, were treated with 2.74 g (126 mmol) $LiBH_4$. The reaction-mixture was stirred under reflux for 6h and then 200 ml of 1N HCl were dropped to the solution under ice-cooling. The mixture was dissolved in ether and washed with water. The solvent was evaporated under reduced pressure yielding 16.2 g (4-Hydroxymethyl-cyclo-hexyl)-methyl-carbamic acid tert-butyl ester.

29.3

To a dry-ice cooled solution of 8.94 ml (125.9 mmol) DMSO in 150 ml CH_2Cl_2 was added 5.95ml (69.24 mmol) oxalylchloride. After 5 min at –78°C, a solution of 16.2 g (66.5 mmol) (4-Hydroxymethyl-cyclo-hexyl)-methyl-carbamic acid tert-butyl ester in 50 ml of CH_2Cl_2, was added slowly. 10 min later, 43.8 ml (314.75 mmol) of Et_3N was added, and the mixture was allowed to attain RT. The mixture was partitioned between Et_2O/1N HCl and water. The solvent was evaporated under reduced pressure yielding 16.12 g of clean (4-Formyl-cyclohexyl)-methyl-carbamic acid tert-butyl ester, MS: 241 (M^+).

29.4

To a solution of 13.71 g (56.8 mmol) (4-Formyl-cyclohexyl)-methyl-carbamic acid tert-butyl ester and 17.8 g (83.46 mmol) triethyl-phosphono-acetat in 150 ml ethanol was added under ice-cooling, 6.0g (110 mmol) NaOMe. After stirring the reaction mixture for 20h at RT, it was concentrated under reduced pressure and then extracted with Et_2O and water. The organic layer was evaporated to dryness and the crude product purified by chromatography on silica gel with EtOAc/Hexane 1:4 yielding 8.4 g of clean 3-[4-(tert-Butoxy carbonyl methyl-amino)-cyclohexyl]-acrylic acid ethyl-ester, MS: 238.

29.5

A solution of 6 g (19.26 mmol) trans-3-[4-(tert-Butoxy carbonyl methyl-amino)-cyclohexyl]-acrylic acid ethyl-ester and 600mg of Pd/C (10 %) was stirred over H_2-atmosphere for 20h. After filtration of the solution, the methanol was evaporated under reduced pressure to yield 5.82 g of clean 3-[4-(tert-Butoxycarbonyl methyl-amino)cyclohexyl]-propanoic acid ethyl-ester. To a solution of this ester in 60 ml of THF was added 917 mg (40 mmol) $LiBH_4$. The solution was refluxed for 8h and then cooled with an ice–bath to 0°C. At this temperature was dropped slowly 1N HCl to the reaction-mixture to destroy excess of $LiBH_4$. The reaction-mixture was diluted with Et_2O and then washed with water. The organic layers were evaporated to dryness to yield 3.39 g of clean trans-[4-(3-Hydroxy-propyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, MS: 271 (M^+).

29.6

1.4 ml (16.24 mmol) oxalylchloride was added to a dry-ice cooled solution (-78°C) of 1.78 ml (25 mmol) DMSO in 40ml CH_2Cl_2. After 10 min. stirring at –78°C, 2.39g (12.49 mmol) of trans-[4-(3-Hydroxy-propyl)-cyclohexyl]-methyl-carbamic acid tert-butyl ester, dissolved in 5 ml CH_2Cl_2, was added. 15 min later, 8.7 ml (62.4 mmol) Et_3N was added and the reaction-mixture was allowed to attain RT. The mixture was diluted with Et_2O and then washed with 1N HCl and water. After evaporation of the solvents, a solution of crude trans-Methyl-[4-(3-oxo-propyl)-cyclohexyl]-carbamic acid tert-butyl ester (3.24 g, 12.02 mmol) and of 2.73 ml (13.3 mmol) triethyl phosphono acetate in 30 ml ethanol, was treated under ice-cooling with 1.37g (24.05 mmol) NaOMe . The solution was stirred for 20h at RT, and then concentrated in vacuo. The crude residue was dissolved in Et_2O and washed with water. The organic layers were concentrated in vacuo and the crude product purified by chromatography on silica gel with EtOAc/Hexane 1:4 to yield 2.46 g of clean trans-5-[4-(tert-Butoxycarbonyl-methyl-amino)-cyclohexyl]-pent-2-enoic acid ethyl ester, MS: 339 (M^+).

29.7

A solution of 2.45 g (7.2 mmol) trans-5-[4-(tert-Butoxycarbonyl-methyl-amino)-cyclohexyl]-pent-2-enoic acid ethyl ester and 200 mg of Pd/C (10%) in 40 ml MeOH was stirred for 20h under H_2-atmosphere. After filtration and evaporation of the methanol under vacuo, 2.39 g 5-[4-(tert-Butoxy carbonyl-methyl-amino)-cyclohexyl]-pentanoic acid ethyl ester could be isolated. 2.05 g (6.0 mmol) of this ester and 470 mg (12 mmol) of $LiAlH_4$ were stirred in 20 ml of THF at RT for 5h. Exess of $LiAlH_4$ was destroyed by adding 10ml of EtOAc and by carefully dropping brine to the reaction-mixture. The solution was dissolved in ether and washed with 1N HCl and water. The organic phase was concentrated under reduced pressure yielding 1.75 g of clean trans-[4-(5-Hydroxy pentyl)-cyclohexyl)-methyl-carbamic acid tert-butyl ester, MS: 300 (M^+).

29.8

To a solution of 1.75 g (5.84 mmol) trans-[4-(5-Hydroxy pentyl)-cyclohexyl)-methyl-carbamic acid tert-butyl ester and 0.5 ml (6.42 mmol) of methan sulfochloride in 20ml CH_2Cl_2 was added, under cooling with an ice bath, 1.56 ml (11.7 mmol) of Et_3N. The mixture was stirred for 3h at RT. The reaction-mixture was then partitioned between ether/1N HCl and water. The ether-solution was concentrated in vacuo to yield 2.12 g of clean Methansulfonic acid trans-5[-4-(tert-butoxy carbonyl-methyl-amino)-cyclohexyl)-pentyl ester.

29.9

200 mg (0.53 mmol) of Methansulfonic acid trans-5[-4-(tert-butoxy carbonyl-methyl-amino)-cyclohexyl)-pentyl ester, dissolved in 2ml of CH_2Cl_2, was treated with 2ml of TFA. After stirring for 20 min at RT, the solution was concentrated in vacuo to yield 245 mg of pure Methansulfonic acid trans-5-(4-methyl amino-cyclohexyl)-pentyl ester·trifluoroacetic acid salt, MS: 278 (MH^+).

29.10

To a solution of 245 mg (0.63 mmol) trans-Methansulfonic acid 5-(4-methyl amino-cyclohexyl)-pentyl ester·trifluoroacetic acid salt and 143.5 mg (0.75 mmol) 4-chlorophenyl chloro formate in 4 ml dioxane, was added at r.t 1.54ml (3.12 mmol) Hünig's base. The mixture was stirred for 1h, then extracted with EtOAc/1N HCl and water. The organic phases were concentrated under reduced pressure and purified by chromatography on silica gel with EtOAc/hexane 1:3 to yield 167 mg of pure trans-[4-(5-Bromo-pentyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester, MS: 432 (MH^+, 1Br).

29.11

A solution of 160 mg (0.37 mmol) trans-[4-(5-Bromo-pentyl)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester and of 0.21 ml N-methyl-N-allyl-amine in 3ml of methanol was stirred over night at 60°C. The solution was concentrated in vacuo, and the residue then purified by chromatography on silica gel with 1N NH_3/methanol 1:10 to yield 110 mg pure trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester, MS: 407 (MH^+, 1Br).

29.12

In analogy to examples 29.10 and 29.11, Methansulfonic acid trans-5-(4-methyl amino-cyclohexyl)-pentyl ester·trifluoroacetic acid salt and 4-trifluoromethyl-phenyl chloro formate were reacted, followed by treatment with N-methyl-N-allyl-amine to yield trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-trifluoromethyl-phenyl ester, MS: 441 (MH^+).

29.13

In analogy to examples 29.10 and 29.11, Methansulfonic acid trans-5-(4-methyl amino-cyclohexyl)-pentyl ester·trifluoroacetic acid salt and 4-trifluoromethyl-phenyl chloro formate were reacted, followed by treatment with 2-ethylamino-ethanol to yield trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-methyl-carbamic acid 4-trifluoromethyl-phenyl ester, MS: 459 (MH^+).

29.14

In analogy to examples 29.10 and 29.11, Methansulfonic acid trans-5-(4-methyl amino-cyclohexyl)-pentyl ester·Trifluoroacetic acid salt and 4-bromophenyl chloro formate were reacted, followed by treatment with N-methyl-N-allyl-amine to yield trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester, MS: 453 (MH^+, 1Br).

29.15

In analogy to examples 29.10 and 29.11, Methansulfonic acid trans-5-(4-methyl amino-cyclohexyl)-pentyl ester·Trifluoroacetic acid salt and 4-bromophenyl chloro formate were reacted, followed by treatment with by 2-ethylamino-ethanol to yield trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-methyl-carbamic acid 4-bromo-phenyl ester, MS: 469 (MH^+, 1Br).

29.16

In analogy to examples 29.10 and 29.11, Methansulfonic acid trans-5-(4-methyl amino-

cyclohexyl)-pentyl ester·Trifluoroacetic acid salt and 3,4-difluoro-phenyl chloro formate were reacted, followed by treatment with N-methyl-N-allyl-amine to yield trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 3,4-difluoro-phenyl ester, MS: 409 (MH^+).

29.17

In analogy to examples 29.10 and 29.11, Methansulfonic acid trans-5-(4-methyl amino-cyclohexyl)-pentyl ester·Trifluoroacetic acid salt and 3,4-difluoro-phenyl chloro formate were reacted, followed by treatment with 2-ethylamino-ethanol to yield trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-methyl-carbamic acid 3,4-difluoro-phenyl ester, MS: 427 (MH^+).

29.18

In analogy to examples 29.10 and 29.11, Methansulfonic acid trans-5-(4-methyl amino-cyclohexyl)-pentyl ester·Trifluoroacetic acid salt and 4-(trifluoromethyl)benzenesulphonyl chloride were reacted, followed by treatment with N-allylmethylamine to yield trans-N-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide, MS: 461 (MH^+).

29.19

In analogy to examples 29.10 and 29.11, Methansulfonic acid trans-5-(4-methyl amino-cyclohexyl)-pentyl ester·Trifluoroacetic acid salt and 4-(trifluoromethyl)benzenesulphonyl chloride were reacted, followed by treatment with 2-ethylamino-ethanol to yield trans-N-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide, MS: 479 (MH^+).

Example 30

To a suspension of 1.39 g (4.4 mmol, 2.2 eq) Hydrogen peroxide·Urea adduct in CH_2Cl_2, 338.5 mg (2.2 mmol, 1.1 eq) phthalic anhydride were added and stirred for 15 min at RT. 800 mg (2.01 mmol) trans-[4-(5-Dimethylamino-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester in CH_2Cl_2 was added and the mixture was stirred at RT for 2h. 5% aqueous K_2CO_3 solution was added and the inorganic phase was extracted with CH_2Cl_2. The organic phases were washed with water and brine and dried over $MgSO_4$. Column chromatography yielded 525 mg (63%) trans-[4-(5-Dimethylamino-pentyloxy)-cyclohexyl]-methyl-carbamic acid 4-chloro-phenyl ester N-oxide as colourless oil, MS: 413 (MH^+, 1Cl).

Example 31

5.85 g (14.71 mmol) of trans-[Toluene-4-sulfonic acid 4-(tert-butoxycarbonyl-methyl-amino)-cyclohexylmethyl ester] (synthesized from trans-(4-Hydroxymethyl-cyclohexyl)-methyl-carbamic acid tert-butyl ester and toluene sulfonyl chloride in pyridine), and 1.45g (29.43 mmol) of sodium cyanide were stirred in 50 ml DMF for 48h at 100 °C. The reaction-mixture was partitioned between ether and water. After drying (Na_2SO_4) and concentration of the ether-phase in vacuo, 3.47 g of crude trans-[(4-Cyanomethyl-cyclohexyl)-methyl-carbamic acid tert-butyl ester] could be isolated. This crude product (14.82 mmol), dissolved in 30ml THF, was treated at –78 °C with 13.5 ml (16.18 mmol) of a 1.2M DIBALH-solution in Toluene. The reaction-mixture was stirred 30 min at –78 °C and 15 min at RT. To the reaction-mixture was then carefully dropped 30 ml of 1N HCl. The reaction-mixture was dissolved in ether and washed with water. The ether-solution was dried (Na_2SO_4) and concentrated under reduced pressure to yield 3.47 g of crude trans-[Methyl-[4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester].

In analogy to examples 29.4 (Horner-Emmons reaction), 29.5 (reduction), 29.8 (mesylation), 29.9 (BOC-deprotection), 29.10 (rection with 4-chlorophenyl chloro formate) and 29.11 (reaction with N-allylmethylamine), trans-[Methyl-[4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid tert-butyl ester] yielded trans-{4-[4-(Allyl-methyl-amino)-butyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester, MS: 393 (MH^+).

Example A

Tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet
Compound of formula I	10.0 - 100.0 mg
Lactose	125.0 mg
Maize starch	75.0 mg
Talc	4.0 mg
Magnesium stearate	1.0 mg

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula I	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

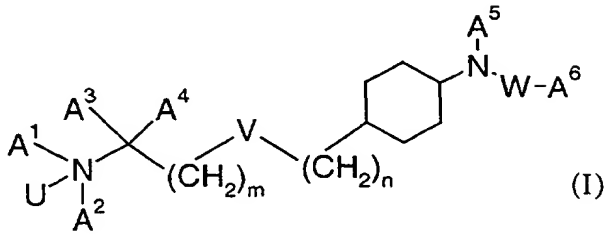
Example C

Injection solutions can have the following composition:

Compound of formula I	3.0 mg
Gelatine	150.0 mg
Phenol	4.7 mg
Water for injection solutions	ad 1.0 ml

Claims

1. Compounds of formula (I)



(I)

wherein

U is O or a lone pair,

V is O, S, $-CH_2-$, $-CH=CH-$, or $-C\equiv C-$,

W is CO, COO, $CONR^1$, CSO, $CSNR^1$, SO_2, or SO_2NR^1,

m and n independently from each other are 0 to 7 and m+n is 0 to 7, with the provisio that m is not 0 if V is O or S,

A^1 is H, lower-alkyl, hydroxy-lower-alkyl, or lower-alkenyl

A^2 is lower-alkyl, cycloalkyl, cycloalkyl-lower-alkyl, or lower-alkenyl, optionally substituted by R^2,

A^3 and A^4 are hydrogen or lower-alkyl, or

A^1 and A^2 or A^1 and A^3 are bonded to each other to form a ring and $-A^1-A^2-$ or $-A^1-A^3-$ are lower-alkylene or lower-alkenylene, optionally substituted by R^2, in which one $-CH_2-$ group of $-A^1-A^2-$ or $-A^1-A^3-$ can optionally be replaced by NR^3, S, or O,

A^5 is H, lower-alkyl, lower-alkenyl, or aryl-lower-alkyl,

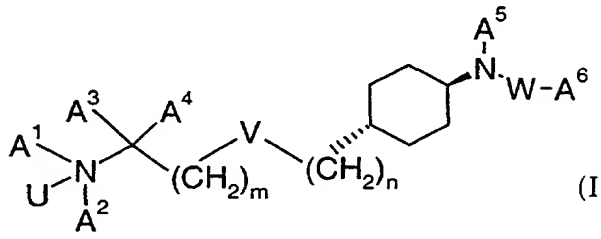
A^6 is lower-alkyl, cycloalkyl, aryl, aryl-lower-alkyl, heteroaryl, heteroaryl-lower-alkyl, lower-alkoxy-carbonyl-lower-alkyl,

R^2 is hydroxy, hydroxy-lower-alkyl, lower-alkoxy, lower-alkoxycarbonyl, $N(R^4,R^5)$, or thio-lower-alkoxy,

R^1, R^3, R^4 and R^5 independently from each other are hydrogen or lower-alkyl,

and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof.

2. Compounds according to claim 1 characterised by formula (Ia)



(Ia)

wherein U, V, W, m, n, A^1, A^2, A^3, A^4, A^5 and A^6 have the significances given in claim 1.

3. Compounds according to any of claims 1 to 2, wherein U is a lone pair.

4. Compounds according to any of claims 1 to 3, wherein V is O, S, -C≡C-, or $-CH_2-$.

5. Compounds according to any of claims 1 to 4, wherein V is O.

6. Compounds according to any of claims 1 to 4, wherein V is $-CH_2-$.

7. Compounds according to any of claims 1 to 6, wherein W is CO, COO, $CONR^1$, $CSNR^1$, SO_2 or SO_2NR^1 and R^1 is hydrogen.

8. Compounds according to any of claims 1 to 7, wherein W is COO or SO_2.

9. Compounds according to any of claims 1 to 8, wherein n is 0 or 1.

10. Compounds according to any of claims 1 to 9, wherein m is 1 to 6, or wherein V is -C≡C- and m is 0.

11. Compounds according to any of claims 1 to 10, wherein A^1 is H, methyl, ethyl, 2-hydroxy-ethyl, or 2-propenyl.

12. Compounds according to any of claims 1 to 11, wherein A^2 is lower-alkyl, cycloalkyl-lower-alkyl, or lower-alkenyl, optionally substituted with R^2, wherein R^2 is hydroxy, methoxy, or ethoxycarbonyl.

13. Compounds according to any of claims 1 to 12, wherein A^2 is methyl, ethyl, 2-hydroxy-ethyl, or 2-propenyl.

14. Compounds according to any of claims 1 to 10, wherein A^1 and A^2 are bonded to each other to form a ring and $-A^1-A^2-$ is lower-alkylene, or lower-alkenylene, optionally

substituted by R^2, in which one $-CH_2-$ group of $-A^1-A^2-$ can optionally be replaced by NR^3, S, or O, wherein R^2 and R^3 are as defined in claim 1.

15. Compounds according to claim 14, wherein A^1 and A^2 are bonded to each other to form a ring and $-A^1-A^2-$ is lower-alkylene, or lower-alkenylene, optionally substituted by R^2, in which one $-CH_2-$ group of $-A^1-A^2-$ can optionally be replaced by O, wherein R^2 is hydroxy or 2-hydroxyethyl.

16. Compounds according to any of claims 1 to 15, wherein A^3 is hydrogen.

17. Compounds according to any of claims 1 to 16, wherein A^4 is hydrogen.

18. Compounds according to any of claims 1 to 17, wherein A^5 is H, lower-alkyl, lower-alkenyl, or benzyl optionally substituted with halogen.

19. Compounds according to any of claims 1 to 18, wherein A^5 is methyl or ethyl.

20. Compounds according to any of claims 1 to 19, wherein A^6 is lower-alkyl, cycloalkyl, phenyl, naphthyl, phenyl-lower-alkyl, pyridyl, indolyl, indolinyl, thienyl, thienyl-methylene, furyl-methylene, benzodioxyl, chinolyl, isoxazolyl, or imidazolyl, optionally substituted by one or more substituents selected from the group consisting of lower-alkyl, lower-alkoxy, lower-alkylcarbonyl, lower-alkoxycarbonyl, fluorine, chlorine, bromine, CN, CF_3, NO_2, or $N(R^6,R^7)$, wherein R^6 and R^7 independently from each other are hydrogen or lower-alkyl.

21. Compounds according to any of claims 1 to 20, wherein A^6 is phenyl optionally substituted by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, and CF_3.

22. Compounds according to any of claims 1 to 21, wherein A^6 is 4-chloro-phenyl, 4-bromo-phenyl, or 4-trifluoromethyl-phenyl.

23. A compounds according to any of claims 1 to 22, selected from the group consisting of

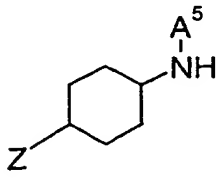
trans-{4-[6-(Allyl-methyl-amino)-hexyloxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,

trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,

trans-N-[4-(6-Diethylamino-hexyloxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,

trans-{4-[4-(Allyl-methyl-amino)-butoxy]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[2-(Allyl-methyl-amino)-ethylsulfanylmethyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-(4-{4-[Ethyl-(2-hydroxy-ethyl)-amino]-butoxy}-cyclohexyl)-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-N-[4-(3-Allylamino-propoxy)-cyclohexyl]-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-methyl-carbamic acid 4-bromo-phenyl ester,
trans-N-(4-{5-[Ethyl-(2-hydroxy-ethyl)-amino]-pentyl}-cyclohexyl)-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-[4-(4-Dimethylamino-butoxy)-cyclohexyl]-methyl-carbamic acid 4-trifluoromethyl-phenyl ester,
trans-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-methyl-carbamic acid 4-bromo-phenyl ester,
trans-{4-[3-(Allyl-methyl-amino)-prop-1-ynyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
trans-N-{4-[5-(Allyl-methyl-amino)-pentyl]-cyclohexyl}-N-methyl-4-trifluoromethyl-benzenesulfonamide,
trans-(4-{3-[Ethyl-(2-hydroxy-ethyl)-amino]-propyl}-cyclohexyl)-methyl-carbamic acid 4-chloro-phenyl ester, and
trans-{4-[4-(Allyl-methyl-amino)-butyl]-cyclohexyl}-methyl-carbamic acid 4-chloro-phenyl ester,
and pharmaceutically acceptable salts thereof.

24. A process for the manufacture of compounds according to any of claims 1 to 23, which process comprises reacting a compound of formula (II)



(II)

wherein

A^5 has the significance given in claim 1,

Z is a group $(A^1,A^2,)N\text{-}C(A^3,A^4)\text{-}(CH_2)_m\text{-}V\text{-}(CH_2)_n$ or $HO\text{-}(CH_2)_n$, wherein A^1, A^2, A^3,A^4, V, m and n have the significances given in claim 1,

with $ClSO_2\text{-}A^6$, $ClCOO\text{-}A^6$, $ClCSO\text{-}A^6$, $OCN\text{-}A^6$, $SCN\text{-}A^6$, $HOOC\text{-}A^6$, or $ClSO_2NR^1\text{-}A^6$.

25. Compounds according to any of claims 1 to 23 when manufactured by a process according to claim 24.

26. Pharmaceutical compositions comprising a compound according to any of claims 1 to 23 and a pharmaceutically acceptable carrier and/or adjuvant.

27. Compounds according to any of claims 1 to 23 for use as therapeutic active substances, particularly as therapeutic active substances for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gall stones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes.

28. A method for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes, which method comprises administering a compound according to any of claims 1 to 23 to a human being or animal.

29. The use of compounds according to any of claims 1 to 23 for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance, and diabetes.

30. The use of compounds according to any of claims 1 to 23 for the preparation of medicaments for the treatment and/or prophylaxis of diseases which are associated with OSC such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and/or treatment and/or prophylaxis of impaired glucose tolerance and diabetes.

31. The novel compounds, processes and methods as well as the use of such compounds substantially as described hereinbefore.

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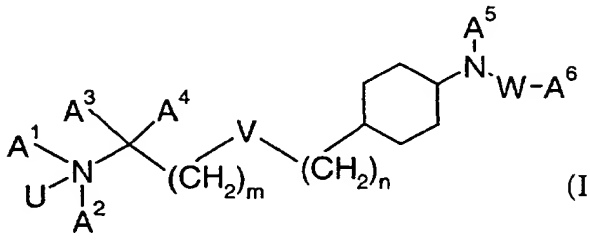
Abstract

The present invention relates to compounds of formula (I)



(I)

wherein U, V, W, A^1, A^2, A^3, A^4, A^5, A^6, m and n are as defined in the description and claims and pharmaceutically acceptable salts and/or pharmaceutically acceptable esters thereof. The compounds are useful for the treatment and/or prophylaxis of diseases which are associated with 2,3-oxidosqualene-lanosterol cyclase such as hypercholesterolemia, hyperlipemia, arteriosclerosis, vascular diseases, mycoses, gallstones, tumors and/or hyperproliferative disorders, and treatment and/or prophylaxis of impaired glucose tolerance and diabetes.

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